BIOLOGICAL MARKERS FOR DIAGNOSING RHEUMATOID ARTHRITIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119 from U.S. Application Ser. No. 60/455,037, filed March 14, 2003, which is incorporated herein in its entirety by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to biological markers for rheumatoid arthritis (RA). More specifically, the present invention relates to the use of such markers to diagnose and treat RA, monitor progression of the disease, evaluate therapeutic interventions, and screen candidate drugs in a clinical or preclinical trial.

BACKGROUND OF INVENTION

[0003] Rheumatoid arthritis (RA) is a chronic inflammatory disorder of the small joints that also has pronounced and potential disabling systemic consequences, including fatigue, malaise and fever. It is estimated that about 2.1 million people in the United States have RA. The disease typically begins in middle age and occurs with increased frequency in older people. For reasons that are not fully understood, about two to three times as many women as men have the disease.

[0004] Although the etiology of the disease is unknown, its pathology evolves with common characteristics over time. The inflamed joint is characterized by synovial fibroblast hyperplasia, infiltration of activated lymphocytes and macrophages, and high levels of neutrophils. Early events are believed to include an inflammatory response initiated by unknown mediators. Activated CD4 T-cells appear to amplify and perpetuate the inflammation. The presence of activated T-cells can induce polyclonal B-cell activation.

[0005] Tissue damage inevitably progresses, releasing autoantigens, and the extent of the T-cell response broadens. Eventually, the constant inflammatory environment may lead to

transformation of the synovial fibroblasts, yielding destructive potential that is independent of T-cells and macrophages. The pro-inflammatory cytokines such as TNF-α, produced mainly by macrophages in the joint, and the cytokines they induce such as IL-6 are systemically active, present in the serum and augment hepatic synthesis of acute-phase proteins. These cytokines are potent stimulators of mesenchymal cells, such as synovial fibroblasts, osteoclasts and chondrocytes, which release tissue-destroying matrix metalloproteinases which ultimately lead to the erosion of bone and cartilage.

[0006] The diagnosis of RA is typically made based on medical history, physical examination and X-ray imaging of the affected joint(s). Antibodies directed to the crystallizable fragment of IgG molecules (rheumatoid factor) are often found in high levels in RA. However, not everyone who has RA tests positive for rheumatoid factor and some who test positive never develop the disease. Neutrophils, for example, are generally elevated in RA, while CD8 T-cells are generally reduced. Also, the CD4:CD8 T-cell ratio is higher in RA subjects. Cush & Lipsky, Arthritis Rheum., 31:1230-8 (1988); Dale, Neutropenia and Neutophilia, in WILLIAMS HEMATOLOGY, Beutler et al., eds., McGraw Hill: New York. p. 823-834 (2001). Other factors associated with RA include, for example, C-reactive protein and antibodies to citrulline-containing peptides. However, there is no consensus panel of RA-specific markers. Early diagnosis and knowledge of disease progression would allow early initiation of treatment when it is most appropriate and potentially would be of the greatest benefit to the patient.

[0007] A number of approaches are used to treat RA. Nonsterioidal anti-inflammatory drugs (NSAIDS) are typically used to reduce pain, swelling and inflammation. Disease-modifying anti-rheumatic drugs (DMARDS) are used to slow progression of the disease and to prevent further joint injury (e.g., gold salts, antimalarials, methotrexate, Penicillamine, Sulfazalazine). The mechanism of action for these drugs is not fully understood. Biologic response modifiers differ from traditional DMARDS in that they target specific constituents of the immune system that contribute to the disease, while leaving other constituents of the immune system intact. This includes anti-TNF alpha inhibitors. While some patients respond well to a particular DMARD or combination of DMARDs, others show only modest benefit or no significant improvement. Furthermore, these drugs are associated with a number of serious side effects. The search for better therapeutics with fewer side effects is a subject of active research.

[0008] Therefore, there is a need to identify biochemical markers for RA. There is also a need for improved compositions and methods for diagnosing RA, and improved compositions and methods for treating RA.

SUMMARY OF THE INVENTION

[0009] One aspect of the invention provides polypeptides that have been identified as differentially expressed in biological samples obtained from RA subjects as compared to samples obtained from non-RA subjects ("polypeptide markers"). The invention also provides polypeptides that have substantial homology with polypeptide markers, modified polypeptide markers, and fragments of polypeptide markers. The invention also includes precursors and successors of the polypeptide markers in biological pathways. The invention also provides molecules that comprise a polypeptide marker, a polypeptide that has substantial homology with a polypeptide marker, a modified polypeptide marker, a fragment of a polypeptide marker, or a precursor or successor of a polypeptide marker (e.g., a fusion protein). As used herein, the term "polypeptides of the invention" shall be understood to refer to any or all of the foregoing polypeptides.

[0010] Another aspect of the invention provides polynucleotides encoding polypeptides of the invention ("polynucleotide markers"). The invention also provides polynucleotides that have substantial homology with polynucleotide markers, modified polynucleotide markers, and fragments of polynucleotide markers. The invention also provides molecules that comprise a polynucleotide marker, a polynucleotide that has substantial homology with a polynucleotide marker, a modified polynucleotide marker or a fragment of a polynucleotide marker (e.g., a vector). Because of the redundancy (degeneracy) of the genetic code, a number of polynucleotides markers are capable of encoding a single polypeptide of the invention. As used herein, the term "polynucleotides of the invention" shall be understood to refer to any or all of the foregoing polynucleotides.

[0011] Another aspect of the invention provides cell populations that have been identified as differentially expressed in biological samples obtained from RA subjects as compared to samples obtained from non-RA subjects. As used herein, the terms "cell

populations of the invention" or "cell population markers" shall be understood to refer to any or all of such cell populations.

[0012] Another aspect of the invention provides antibodies that selectively bind to a polypeptide of the invention, polynucleotide of the invention, or a cell population of the invention (e.g., a molecule associated with a cell that is a member of a cell population). The invention also provides methods for producing an antibody that selectively binds to a polypeptide of the invention, polynucleotide of the invention, or cell population of the invention.

[0013] Another aspect of the invention provides compositions comprising (i) a polypeptide of the invention, (ii) a polynucleotide of the invention, (iii) an antibody against a polypeptide of the invention, polynucleotide of the invention or cell population of the invention, (iv) an inhibitor of the activity of a polypeptide of the invention, a polynucleotide of the invention or a cell population of the invention, or (v) a molecule that can increase or decrease the level or activity of a polypeptide of the invention, a polynucleotide of the invention or a cell population of the invention. Such compositions may be pharmaceutical compositions formulated for use as therapeutics.

[0014] Another aspect of the invention provides a method for detecting the level or activity of a polypeptide of the invention, a polynucleotide of the invention or a cell population of the invention. In one embodiment, for example, the method comprises contacting an antibody that selectively binds to a polypeptide of the invention with a biological sample suspected of containing such polypeptide under conditions that would permit the formation of a stable complex and detecting any stable complexes that are formed. In another embodiment, the method comprises determining the activity of a polypeptide of the invention that functions as an enzyme. In another embodiment, the method comprises determining the level of a polynucleotide of the invention in a cell obtained from the subject.

[0015] Another aspect of the invention provides a method for diagnosing RA in a subject by detecting the level or activity of a polypeptide of the invention, a polynucleotide of the invention, or a cell population of the invention in a biological sample obtained from the subject. For example, in one embodiment, the method comprises obtaining a biological sample from a subject suspected of having RA, or at risk for developing RA, and comparing the level of a

polypeptide of the invention in the biological sample with the level or activity in a biological sample obtained from a non-RA subject or with a standard value or reference range. In some embodiments, the method is used for staging or stratifying subjects with RA, monitoring progression of the disease, response to therapy, or susceptibility to RA. In some embodiments, a plurality of polypeptides of the invention, polynucleotides of the invention, or cell populations of the invention are detected. In some embodiments, such plurality of polypeptides of the invention, polynucleotides of the invention, or cell populations, are detected in a pattern (e.g., two specific polypeptide markers are elevated and one specific cell population is decreased). In some embodiments, the method comprises detecting known markers of RA or considering other clinical indicia of RA in addition to detecting one or more polypeptides of the invention, polynucleotides of the invention or cell populations of the invention. Another aspect of the invention provides methods for monitoring therapeutic treatment of RA.

[0016] Another aspect of the invention provides methods for treating RA by administering to a subject a therapeutic agent that results in an increase or decrease in the level or activity of a polypeptide of the invention, a polynucleotide of the invention or a cell population of the invention (e.g., the level of a certain polypeptide marker in a sample obtained from the subject). In one embodiment, the therapeutic agent administered to the subject is one or more markers of the invention. For polypeptides of the invention, polynucleotides of the invention, or cell populations of the invention that are increased in biological samples obtained from RA subjects, the method comprises administering a therapeutic agent that decreases the level or activity of the polypeptide, polynucleotide or cell population. For polypeptides of the invention, polynucleotides of the invention, or cell populations of the invention that are decreased in biological samples obtained from RA subjects, the method comprises administering a therapeutic agent that increases the level or activity of the polypeptide, polynucleotide, or cell population.

[0017] Another aspect of the invention provides a method for screening a candidate compound for use as a therapeutic agent for treating RA. In one embodiment, the method comprises administering the candidate compound to an RA subject and screening for the ability to increase or decrease the level or activity of a polypeptide of the invention, a polynucleotide of

the invention, or a cell population of the invention in a biological sample obtained from the subject.

[0018] Another aspect of the invention provides a kit for performing one or more of the methods described above. In another embodiment, the kit is for detecting the level or activity of a polypeptide of the invention, a polynucleotide of the invention, or a cell population of the invention and includes an antibody that selectively binds to the polypeptide, polynucleotide or cell population.

[0019] Other features and advantages of the invention will become apparent to one of skill in the art from the following description and claims.

DETAILED DESCRIPTION OF THE INVENTION

[0020] The present inventors have discovered polypeptides, polynucleotides, and cell populations that are differentially expressed in biological samples obtained from RA subjects compared to samples obtained from non-RA subjects. The levels and activities of these polypeptides, polynucleotides, and cell populations can be used as biological markers indicative of rheumatoid arthritis (RA).

[0021] According to one definition, a biological marker is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to therapeutic interventions." NIH Biomarker Definitions Working Group (1998). Biological markers can also include patterns or ensembles of characteristics indicative of particular biological processes ("panel of markers"). The marker measurement can be increased or decreased to indicate a particular biological event or process. In addition, if a marker measurement typically changes in the absence of a particular biological process, a constant measurement can indicate occurrence of that process.

[0022] Marker measurements may be of the absolute values (e.g., the molar concentration of a molecule in a biological sample) or relative values (e.g., the relative concentration of two molecules in a biological sample). The quotient or product of two or more measurements also may be used as a marker. For example, some physicians use the total blood cholesterol as a marker of the risk of developing coronary artery disease, while others use the

ratio of total cholesterol to HDL cholesterol. See discussion of marker measurement and discovery in Ringold et al., "Phenotype and Biological Marker Identification System" WO 00/65472 (published Nov. 2, 2000), incorporated herein by reference in its entirety.

[0023] In the invention, the markers are primarily used for diagnostic purposes. However they may also be used for therapeutic, drug screening and patient stratification purposes (e.g., to group patients into a number of "subsets" for evaluation), as well as other purposes described herein, including evaluation the effectiveness of an RA therapeutic.

[0024] The practice of the invention employs, unless otherwise indicated, conventional methods of analytical biochemistry, microbiology, molecular biology and recombinant DNA generally known techniques within the skill of the art. Such techniques are explained fully in the literature. (See, e.g., Sambrook et al. Molecular Cloning: A Laboratory Manual. 3rd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2000; DNA Cloning: A Practical Approach, Vol. I & II (Glover, ed.); Oligonucleotide Synthesis (Gait, ed., Current Edition); Nucleic Acid Hybridization (Hames & Higgins, eds., Current Edition); Transcription and Translation (Hames & Higgins, eds., Current Edition); CRC Handbook of Parvoviruses, Vol. I & II (Tijessen, ed.); Fundamental Virology, 2nd Edition, Vol. I & II (Fields and Knipe, eds.)).

[0025] The terminology used herein is for describing particular embodiments and is not intended to be limiting. As used herein, the singular forms "a," "and" and "the" include plural referents unless the content and context clearly dictate otherwise. Thus, for example, a reference to "a marker" includes a combination of two or more such markers.

[0026] Unless defined otherwise, all scientific and technical terms are to be understood as having the same meaning as commonly used in the art to which they pertain. For the purposes of the invention, the following terms are defined below.

I. Definitions

[0027] As used herein, the term "antibody" refers to any molecule that reversibly binds to another with the required selectivity. Thus, the term includes any molecule that is capable of selectively binding to a marker of the invention. The term includes an immunoglobulin molecule

capable of binding an epitope present on an antigen. The term is intended to encompasses not only intact immunoglobulin molecules such as monoclonal and polyclonal antibodies, but also bi-specific antibodies, humanized antibodies, chimeric antibodies, anti-idiopathic (anti-ID) antibodies, single-chain antibodies, Fab fragments, F(ab') fragments, fusion proteins and any modifications of the foregoing that comprise an antigen recognition site of the required selectivity (see "selectively binding" defined, infra). The term also includes non-immunoglobin species. Thus, for example, a binding molecule may be a member of a binding pair such as enzyme with respect to a substrate, substrate with respect to an enzyme, lectin with respect to a carbohydrate, carbohydrate with respect to a lectin, receptor with respect to a hormone, hormone with respect to a receptor, ligand with respect to a counterligand, counterligand with respect to a ligand, aptamer with respect to its target, target with respect to its aptamer, and so on. Consistent with the foregoing, an "antibody" described as selectively binding to a polypeptide of the invention should be understood as including any molecule that reversibly binds to the polypeptide with the required selectivity.

[0028] As used herein, the term "biological sample" means any biological substance, including but not limited to blood (including whole blood, leukocytes prepared by lysis of red blood cells, peripheral blood mononuclear cells, plasma and serum), sputum, urine, semen, cerebrospinal fluid, bronchial aspirate, sweat, feces, synovial fluid, cells, and whole or manipulated tissue.

[0029] As used herein, the term "cell population" means a set of cells having characteristics in common. The characteristics include without limitation the presence and level of one, two, three or more cell-associated molecules (e.g., cell-surface antigens). One, two, three or more cell-associated molecules can thus define a cell population.

[0030] As used herein, the term "cell-associated molecule" means any molecule associated with a cell. This includes without limitation (i) intrinsic cell surface molecules such as proteins, glycoproteins, lipids, and glycolipids; (ii) extrinsic cell surface molecules such as cytokines bound to their receptors, immunoglobulin bound to Fc receptors, foreign antigen bound to B-cell or T-cell receptors and auto-antibodies bound to self antigens; (iii) intrinsic internal molecules such as cytoplasmic proteins, carbohydrates, lipids and mRNA, and nuclear

protein and DNA (e.g., genomic and somatic nucleic acids); and (iv) extrinsic internal molecules such as viral proteins and nucleic acid. As an example, there are hundreds of leukocyte cell surface proteins or antigens, including leukocyte differentiation antigens (e.g., CD antigens), antigen receptors (e.g., B-cell receptor and T-cell receptor) and major histocompatibility complexes. Each of these classes encompasses a vast number of proteins.

[0031] As used herein, the term "differentially expressed" refers to the level or activity of a constituent in a first sample (or set of samples) as compared to the level or activity of the constituent in a second sample (or set of samples), where the method used for detecting the constituent provides a different level or activity when applied to the two samples (or sets of samples). Thus, for example, a polypeptide of the invention that is measured at one concentration in a first sample, and at a different concentration in a second sample is differentially expressed in the first sample as compared with the second sample. A marker would be referred to as "increased" in the first sample if the method for detecting the marker indicates that the level or activity of the marker is higher or greater in the first sample than in the second sample (or if the marker is detectable in the first sample but not in the second sample). Conversely, the marker would be referred to as "decreased" in the first sample if the method for detecting the marker indicates that the level or activity of the marker is lower in the first sample than in the second sample (or if the marker is detectable in the second sample but not in the first sample). In particular, a marker is referred to as "increased" or "decreased" in a sample (or set of samples) obtained from a subject (e.g., an RA subject, a subject suspected of having RA, a subject at risk of developing RA) if the level or activity of the marker is higher or lower, respectively, compared to the level of the marker in a sample (or set of samples) obtained from another subject (e.g., a non-RA subject) or subjects or a reference value or range.

[0032] As used herein, the terms "fold increase" and "fold decrease" refer to the relative increase or decrease in the level or activity of a marker in one sample (or set of samples) compared to another sample (or set of samples). A positive fold change indicates an increase in the level of a marker while a negative fold change indicates a decrease in the level of a marker. The increase or decrease may be measured by any method or technique known to those of skill in the art. As will be appreciated by one of skill in the art, the observed increase or decrease may vary depending on the particular method or technique that is used to make the measurement.

[0033] As used herein, the term "fragment" as applied to a polypeptide (e.g., "a fragment of a polypeptide") refers to a single amino acid of a full-length polypeptide from which it has been derived or to a polymer of amino acid residues comprising an amino acid sequence that has at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 20 contiguous amino acid residues or at least 30 contiguous amino acid residues of a sequence of the full-length polypeptide from which it has been derived. As used herein, the term "fragment" as applied to a polynucleotide (e.g., "a fragment of a polynucleotide") refers to a single nucleic acid of a full-length polynucleotide or to a polymer of nucleic acid residues comprising a nucleic acid sequence that has at least 15 contiguous nucleic acid residues, at least 30 contiguous nucleic acid residues, at least 60 contiguous nucleic acid residues of a sequence of a full-length polynucleotide from which it has been derived.

[0034] As used herein, the term "isolated" as applied to a molecule or cell refers to a molecule or cell that has been removed from its natural environment. For example, a polypeptide can be considered isolated if it is separated from one or more metabolites, polynucleotides and other polypeptides with which it is naturally associated. Isolated molecules can be either prepared synthetically or purified from their natural environment (e.g., biological sample obtained from a subject). Standard methodologies known in the art can be employed to obtain and isolate the polynucleotides, polypeptides, antibodies, other molecules, and cells of the invention. The term "isolated" does not necessarily reflect the extent to which the molecule or cell has been purified.

[0035] As used herein, the term "marker" includes polypeptide markers, polynucleotide markers, and cell population markers. For clarity of disclosure, aspects of the invention will be described with respect to "polypeptide markers," "polynucleotide markers" and "cell population markers." However, statements made herein with respect to "polypeptide markers" are intended to apply to other polypeptides of the invention. Likewise, statements made herein with respect to "polynucleotide markers" are intended to apply to other polynucleotides of the invention. Thus, for example, a polynucleotide described as encoding a "polypeptide marker" is intended to encompass a polynucleotide that encodes a polypeptide marker, a polypeptide that has substantial homology to a polypeptide marker, a modified polypeptide marker, a fragment, precursor or successor of a polypeptide marker, and molecules that comprise a polypeptide

marker, homologous polypeptide, a modified polypeptide marker or a fragment, precursor or successor of a polypeptide marker. Furthermore, consistent with their definition, supra, as sets of cells having characteristics in common, statements made herein with respect to "cell population markers (or "cell populations of the invention") are intended also to apply to one or more cells that are members of the cell populations. Thus, for example, an antibody described as selectively binding to a "cell population of the invention" should be understood as including an antibody that selectively binds to a cell that is a member of the cell population.

[0036] As used herein, the phrase "capable of performing the function of that polypeptide in a functional assay" means that the polypeptide has at least 50% of the activity, at least 60% of the activity, at least 70% of the activity, at least 80% of the activity, at least 90% of the activity, or at least 95% of the activity of the polypeptide in the functional assay.

[0037] As used herein, the term "polypeptide" refers to a single amino acid or a polymer of amino acid residues of any length. A polypeptide includes without limitation an amino acid, an oligopeptide, a peptide and a protein. A polypeptide may be composed of a single polypeptide chain or two or more polypeptide chains. A polypeptide can be linear or branched. A polypeptide can comprise modified amino acid residues, amino acid analogs or non-naturally occurring amino acid residues and can be interrupted by non-amino acid residues. Included within the definition are amino acid polymers that have been modified, whether naturally or by intervention (e.g., formation of a disulfide bond, glycosylation, lipidation, methylation, acetylation, phosphorylation, conjugation with a labeling molecule).

[0038] As used herein, the term "polynucleotide" refers to a single nucleotide or a polymer of nucleic acid residues of any length. The polynucleotide may contain deoxyribonucleotides, ribonucleotides, and/or their analogs and may be double-stranded or single stranded. A polynucleotide can comprise modified nucleic acids (e.g., methylated), nucleic acid analogs or non-naturally occurring nucleic acids and can be interrupted by non-nucleic acid residues. Analogs of both the purine and pyrimidine base can differ from a corresponding naturally occurring moiety by having new substituent groups attached thereto, for example, 2,6-diaminopurine or didehydroribose, by having naturally occurring substituent groups deleted therefrom, or by having atoms normally present replaced by others, for example, 8-azaguanine.

Polynucleotides can also comprise modified backbones, including, but not limited to, methyl phosponates, phosphorothioates, phosphordithioates, and PNA backbones. For example a polynucleotide includes a gene, a gene fragment, cDNA, isolated DNA, mRNA, tRNA, rRNA, isolated RNA of any sequence, recombinant polynucleotides, primers, probes, plasmids, and vectors. Included within the definition are nucleic acid polymers that have been modified, whether naturally or by intervention, including by *in vitro* manipulation). For every single-stranded polynucleotide of the invention, the invention also includes the complementary polynucleotide.

[0039] In some embodiments, a polypeptide marker or a polynucleotide marker is part of one or more biological pathways (e.g., amino acid metabolism, the urea cycle, the citric acid cycle, pentose phosphate pathway, glycogen synthesis and degradation pathways, fatty acid synthesis and breakdown pathways, prostaglandin and steroid biosynthesis, purine and pyrimidine synthesis, deoxyribonucleotide synthesis). The identification of such biological pathways and their members is within the skill of one in the art. Once a polypeptide of the invention or polynucleotide of the invention is identified as part of one or more biological pathways, the invention includes additional members of the pathway that precede or follow the polypeptide or polynucleotide by one step, two steps, three steps, or more steps. As used herein, the term "precursor" or "metabolic precursor" refers to a molecule (or reactant) that precedes the marker in the pathway while the term "successor" or "metabolic successor" refers to a molecule (or product) that follows the marker in the pathway.

[0040] As used herein, the terms "RA subject" and "a subject who has RA" refer to a subject who has been diagnosed with RA. The terms "non-RA subject" and "a subject who does not have RA" are refer to a subject who has not been diagnosed as having RA. Non-RA subjects may be healthy and have no other disease, or they may have a disease other than RA. While human subjects are described herein, it is to be understood that in some embodiments, subject refers to a laboratory animal.

[0041] As used herein, the term "selectively binding," refers to the ability of antibodies to preferentially bind to an antigen (i.e., to be able to distinguish that antigen from unrelated constituents in a mixture). The antigen may be free of other constituents or part of a complex,

such as associated with a cell. Binding affinities, commonly expressed as equilibrium association constants, typically range from about 10^3 M^{-1} to about 10^{12} M^{-1}. Binding can be measured using a variety of methods known to those skilled in the art including immunoblot assays, immunoprecipitation assays, radioimmunoassays, enzyme immunoassays (e.g., ELISA), immunofluorescent antibody assays and immunoelectron microscopy. See, e.g., Sambrook et al., supra.

[0042] As used herein, the term "stringent hybridization conditions" refers to standard hybridization conditions under which polynucleotides are used to identify molecules having similar nucleic acid sequences. Such standard conditions are disclosed, for example, in Sambrook et al., supra. Stringent hybridization conditions typically permit isolation of polynucleotides having at least 70% nucleic acid sequence identity, at least 80% nucleic acid sequence identity, at least 90% nucleic acid sequence identity, at least 95% nucleic acid sequence identity or at least 99% nucleic acid sequence identity with the polynucleotide being used to probe in the hybridization reaction. Formulae to calculate the appropriate hybridization and wash conditions to achieve hybridization permitting 30% or fewer mismatches of nucleotides are disclosed, for example, in Meinkoth et al., Anal. Biochem. 138:267-284 (1984), incorporated herein by reference in its entirety.

[0043] As used herein, the term "substantially homologous" (or "substantial homology" or a "homolog") as applied to two or more polypeptides means (i) that there is at least 70% homology, at least 80% homology, at least 90% homology, at least 95% homology or at least 99% homology between their amino acid sequences, or (ii) that a polynucleotide encoding one of the polypeptides is capable of forming a stable duplex with the complementary sequence of a polynucleotide encoding the other polypeptide. As used herein, the term "substantially homologous" (or "substantial homology" or a "homolog") as applied to two or more polynucleotides means (i) that there is at least 70% homology, at least 80% homology, at least 90% homology, at least 95% homology or at least 99% homology between their amino acid sequences, or (ii) that one or more strands of one of the polynucleotides are capable of forming a stable duplex with one or more strands of the other.

II. Polypeptide and Metabolite Markers

[0044] One embodiment of the invention is based, in part, on the discovery that certain polypeptide markers are differentially expressed in biological samples obtained from RA subjects compared to biological samples obtained from non-RA subjects and, in particular, that such differences are statistically significant.

[0045] A high molecular weight fraction, containing proteins with molecular weights greater than about 5-kDa, was separated from serum samples, individually, obtained from RA subjects and serum samples obtained from non-RA subjects. After removal of high abundance proteins, the high molecular weight fraction was digested with trypsin. The high molecular weight fraction was then separated by chromatographic means and analyzed by mass spectrometry. The resulting spectra were compared to identify peaks that were associated with markers differentially expressed in subjects with RA. In some cases, peaks associated with markers differentially expressed in subjects with RA were further investigated to identify the polypeptide markers represented by the peak. Wang et al., Anal. Chem., 75:4818-4826 (2003).

[0046] Table 1 lists the full-length proteins for which a plurality of fragments were identified as differentially expressed (significantly increased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0047] Table 2 lists the full-length proteins for which a plurality of fragments were identified as differentially expressed (significantly decreased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0048] Table 3 lists polypeptides that were identified as differentially expressed (significantly increased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0049] Table 4 lists polypeptides that were identified as differentially expressed (significantly decreased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0050] Table 5 lists additional polypeptides that were identified as differentially expressed (significantly increased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0051] Table 6 lists additional polypeptides that were identified as differentially expressed (significantly decreased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0052] The polypeptide markers of the invention that are set forth in Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6 are each described by (i) the mass to charge ratio (m/z), (ii) the chromatographic retention time (R.T.), (iii) the charge state of a molecular ion (z), (iv) the protonated parent mass (M+H), (v) the expression ratio (exp. ratio), which is a ratio of mean group intensities indicating the relative normalized signal for RA subject group compared to non-RA subject group, (vi) fold change, and (v) the applicable p-value range. The polypeptide markers set forth in Table 1, Table 2, Table 5 and Table 6 are also described by their corresponding identification number from NCBI's reference sequence database (Accession # and gi #) and additional identifying information (e.g., the name or sequence of the peptide marker as contained in the NCBI queried database and database searching using the TurboSEQUEST and Mascot software programs). As one of skill in the art will appreciate, the physical and chemical properties presented in the Tables is sufficient to distinguish the polypeptides from other materials; in particular, the polypeptides are uniquely identified by M+H value, as well as the m/z value and R.T. values within the given experimental platform (see Examples).

[0053] Some variation is inherent in the measurements of physical and chemical characteristics of the markers. The magnitude of the variation depends to some extent on the reproducibility of the separation means and the specificity and sensitivity of the detection means used to make the measurement. Preferably, the method and technique used to measure the markers is sensitive and reproducible. The m/z and R.T. values may vary to some extent depending on a number of factors relating to the protocol used for the chromatography and the mass spectrometry parameters (e.g., solvent composition, flow rate). As one of skill in the art will appreciate, the data set forth in the Tables (e.g., M+H values) reflects to some extent the equipment and conditions used to make the measurements. The values stated in the Tables were

obtained using the equipment and conditions described in the Examples. When a sample is processed and analyzed in this manner, the retention time of a marker is about the value stated for the marker and the marker has a mass-to-charge ratio of about the value stated for the marker.

[0054] The polypeptide markers of the invention are useful in methods for diagnosing RA, determining the extent and/or severity of the disease, monitoring the progression of the disease and/or response to therapy. The markers are also useful in methods for treating RA and for evaluating the efficacy of treatment. The markers may be targets for treatment. The markers may also be used as pharmaceutical compositions or in kits. The markers may also be used to screen candidate compounds that modulate the level or activity of the markers. The markers may also be used to screen candidate drugs for their ability to treat RA.

[0055] In one embodiment, the invention provides a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6. In another embodiment, the invention provides a molecule that comprises such a polypeptide marker.

[0056] In another embodiment, the invention provides a polypeptide that is substantially homologous to a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6. In another embodiment, the invention provides a molecule that comprises such a polypeptide.

[0057] In another embodiment, the invention provides a polypeptide having an M+H value of about the value stated for a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6. In another embodiment, the invention provides a molecule that comprises such a polypeptide.

[0058] In another embodiment, the invention provides a polypeptide having an M+H value within 1.0% (more particularly within 0.5%, more particularly within 0.1%, more particularly, within 0.05%, more particularly within 0.01%) of the M+H value stated for a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6. In another embodiment, the invention provides a molecule that comprises such a polypeptide.

[0059] In another embodiment, the invention provides a polypeptide that is a fragment, precursor, successor or modified version of a polypeptide marker described in Table 1, Table 2,

Table 3, Table 4, Table 5 or Table 6. In another embodiment, the invention provides a molecule that comprises such a polypeptide.

[0060] In another embodiment, the invention provides a polypeptide that is structurally different from a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6 but is capable of performing the function of that polypeptide marker in a functional assay. For example, such a polypeptide may have amino acid sequence that is changed only in nonessential amino acid residues from a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6. In another embodiment, the invention provides a molecule that comprises such a polypeptide.

[0061] Polypeptides of the invention may be isolated by any suitable method known in the art. Native polypeptide markers can be purified from natural sources by standard methods known in the art (e.g., chromatography, centrifugation, differential solubility, immunoassay). In one embodiment, polypeptide markers may be isolated from a serum sample using the chromatographic methods disclosed herein. In another embodiment, polypeptide markers may be isolated from a sample by contacting the sample with substrate-bound antibodies that selectively bind to the polypeptide marker. Alternatively, an isolated polypeptide marker can be produced using recombinant DNA technology or chemical synthesis.

[0062] An isolated polypeptide of the present invention can be produced in a variety of ways. Given the amino acid sequence or the corresponding DNA, cDNA, or mRNA that encodes them, polypeptides markers may be synthesized using recombinant or chemical methods. For example, polypeptide markers can be produced by transforming a host cell with a nucleotide sequence encoding the polypeptide marker and cultured under conditions suitable for expression and recovery of the encoded protein from the cell culture. See, e.g., Hunkapiller et al., Nature 310:105-111 (1984). Polypeptides of the present invention can be purified using a variety of standard protein purification techniques.

III. Polynucleotides Encoding Polypeptide Markers

[0063] In one aspect, the invention provides a polynucleotide that encodes the polypeptides of the invention. Such polynucleotides include without limitation genomic DNA, cDNA and mRNA transcripts.

[0064] In one embodiment, the invention provides a polynucleotide that encodes a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that encodes a molecule that comprises such a polypeptide marker.

[0065] In another embodiment, the invention provides a polynucleotide that encodes a polypeptide that is substantially homologous to a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that encodes a molecule that comprises such a polypeptide.

[0066] In another embodiment, the invention provides a polynucleotide that encodes a polypeptide having an M+H value of about the value stated for a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that encodes a molecule that comprises such a polypeptide.

[0067] In another embodiment, the invention provides a polynucleotide that encodes a polypeptide having an M+H value within 1% (more particularly within 0.5%, more particularly within 0.1%, more particularly, within 0.05%, more particularly within 0.01% of the M+H value stated for a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6, or that encodes a molecule that comprises such a polypeptide.

[0068] In another embodiment, the invention provides a polynucleotide that encodes a polypeptide that is a fragment, precursor, successor or modified version of a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6, or that encodes a molecule that comprises such a polypeptide.

[0069] In another embodiment, the invention provides a polynucleotide that encodes a polypeptide that is structurally different from a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6 but is capable of performing the function of that

polypeptide marker in a functional assay, or that encodes a molecule that comprises such a polypeptide.

[0070] In another embodiment, the invention provides a polynucleotide that is a fragment or modified version or is substantially homologous to any of the above-described polynucleotides.

[0071] Many of the polypeptides listed in Table 3, Table 4, Table 5 and Table 6 are fragments of full-length proteins, either because they were present as such in the serum sample or as a result of the trypsin digestion that was performed during the processing of the serum samples. In many cases, the sequence of the full-length protein can be ascertained from the amino acid sequence of the fragment by searching a protein sequence database. In any event, the full-length proteins comprising the fragments are included within the scope of the polypeptides of the invention.

[0072] Polynucleotides that encode polypeptides of the invention can be used to screen existing genomic, cDNA or expression libraries to find the gene that encodes the polynucleotide of the invention. A library is typically screened using a probe that is complementary either to (i) the polynucleotide that encodes a polypeptide of the invention or (ii) the complement of such polynucleotide. Hybridization is monitored by any suitable method known in the art. Once located, the gene that encodes a polynucleotide of the invention can be cloned. The protein product of such a gene is included within the scope of the polypeptides of the invention.

[0073] Alternatively, the sequence of the polynucleotide that encodes a polypeptide of the invention can be used to search public or private computer databases (e.g., SWISS-PROT, GenBank) that will provide the gene sequence (or gene sequences) comprising the polynucleotide sequence and/or the amino acid sequence of the gene product.

[0074] The polynucleotides of the invention can be used to synthesize the polypeptides of the invention. In addition, the polynucleotides of the invention may be measured instead of (or in addition to) the polypeptides of the invention in a method of the invention. Thus, for example, if the level of a polypeptide marker is increased in RA-subjects, an increase in the level of the mRNA that encodes the polypeptide marker may be used, rather than the level of the polypeptide

marker (e.g., to diagnose RA in the subject). As one of skill in the art will recognize, however, the level of mRNA is typical not directly proproportional to the level of protein, even in a given cell. Furthermore, mRNA level will not indicate post-translational modifications of the protein.

[0075] Polynucleotide markers may be isolated by any suitable method known in the art. A native polynucleotide of the invention can be obtained from its natural source by standard methods known in the art (e.g., chromatography, centrifugation, differential solubility, immunoassay). In one embodiment, a polynucleotide marker may be isolated from a mixture by contacting the mixture with substrate bound probes that are complementary to the polynucleotide marker under hybridization conditions.

[0076] Alternatively, an isolated polynucleotide of the invention may be produced by any suitable chemical or recombinant method known in the art. In one embodiment, for example, a polypeptide marker can be produced using polymerase chain reaction (PCR) amplification. In another embodiment, a polynucleotide marker can be synthesized from appropriate reactants using the methods and techniques of organic chemistry.

IV. Cell Populations

[0077] One embodiment of the invention is based, in part, on the discovery that certain cell populations are differentially expressed in biological samples obtained from RA subjects compared to biological samples obtained from non-RA subjects and, in particular, that such differences are statistically significant.

[0078] A large number of cellular variables were analyzed, including cell counts, cell ratios, and the level of cell-associated molecules, using microvolume laser scanning cytometry (MLSC). Walton et al., Proc.SPIE-Int.Soc.Opt.Eng., 3926:192-201 (2000). Blood samples obtained from RA subjects and non-RA subjects were stained with fluorophore-labeled antibodies specific for cell surface antigens and loaded into optical-quality capillary arrays. Typically, three antibody reagents, each with a different fluorescent tag and each detected in a different channel, were used per assay. Each assay typically contained one or two antibodies to the major cell populations (neutrophils, eosinophils, monocytes, total T-cells, CD4 T-cells, B-cells and NK cells) and one or two antibodies to subsetting antigens that may indicate the

functional state, activation state or adhesion characteristics of the population. The capillary was imaged and the fluorescent events were detected. Peaks corresponding to antibody-labeled cells were identified with image processing software. See, Norton et al. Prof.SPIE-Int.Soc.Opt.Eng., 3921:20-30 (2000), incorporated herein by reference in its entirety. Unlabeled cells (e.g., erythrocytes and leukocytes not expressing the target antibodies) were not identified. Compensation was made for spectral overlap of the dyes with respect to the intensity data, so result values were proportional to the amount of dye-antibody reagent on each cell. Because the volume of the scan is precisely defined, absolute cell counts (cells per μL of blood) were determined.

[0079] Table 7 lists the cell populations that were identified as differentially expressed (significantly increased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0080] Table 8 lists cell populations that were identified as differentially expressed (significantly decreased) in serum samples obtained from RA subjects compared with serum samples obtained from non-RA subjects.

[0081] The cell population markers set forth in Table 7 and Table 8 are each described by (i) general cell type, (ii) assay, (iii) cell population, (iv) property (i.e., count, ratio, or relative antigen intensity); (v) p-value (either adjusted or univariate, as appropriate depending on the normality of the data), and (vi) the effect size (difference of means between the two groups divided by the weighted standard deviation) which indicates how well the groups are separated.

[0082] Some variation is inherent in the measurement of the levels of the cell population markers. The magnitude of the variation depends to some extent on the reproducibility of the sample preparation procedures and on the specificity and sensitivity of the detection means used to make the measurement. Preferably, the method and technique used to measure the cell population makers is sensitive and reproducible. As one of skill in the art will appreciate, the data set forth in Tables 7 and 8 reflects to some extent the equipment and conditions used to make the measurements. The values stated in the Tables were obtained using the equipment and conditions described in the Examples. When a sample is processed and analyzed in this manner,

the values are about those stated for the marker (within about 10%, within about 5%, within about 1% of the value stated).

[0083] The cell population markers of the invention are useful in methods for diagnosing RA, determining the extent and/or severity of the disease, monitoring the progression of the disease and/or response to therapy. The markers are also useful in methods for evaluating the efficacy of treatment for RA. The cell population markers can also be used in kits. The cell population markers may also be used to screen candidate compounds that modulate the expression of the markers. The cell population markers may also be used to screen candidate drugs for their ability to treat RA.

V. <u>Antibodies</u>

[0084] In one aspect, the invention provides antibodies that selectively bind to a polypeptide of the invention, a polynucleotide of the invention, or a cell population of the invention (e.g., to a cell-surface antigen).

[0085] In one aspect, the invention provides an antibody that selectively binds to a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that selectively binds to a molecule that comprises such a polypeptide marker.

[0086] In another embodiment, the invention provides an antibody that selectively binds to a polypeptide that is substantially homologous to a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that selectively binds to a molecule that comprises such a polypeptide.

[0087] In another embodiment, the invention provides an antibody that selectively binds to a polypeptide having an M+H value of about the value stated for a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that selectively binds to a molecule that comprises such a polypeptide.

[0088] In another embodiment, the invention provides an antibody that selectively binds to a polypeptide having an M+H value within 1% (more particularly within 0.5%, more particularly within 0.1%, more particularly, within 0.05%, more particularly within 0.01% of the

M+H value stated for a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that selectively binds to a molecule that comprises such a polypeptide.

[0089] In another embodiment, the invention provides an antibody that selectively binds to a polypeptide that is a fragment, precursor, successor or modified version of a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or that selectively binds to a molecule that comprises such a polypeptide.

[0090] In another embodiment, the invention provides an antibody that selectively binds to a polypeptide that is structurally different from a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6 but is capable of performing the function of that polypeptide marker in a functional assay, or that selectively binds to a molecule that comprises such a polypeptide.

[0091] In another embodiment, the invention provides an antibody that selectively binds to a polynucleotide that encodes a polypeptide of the invention, or that selectively binds to a molecule that comprises such a polynucleotide.

[0092] In another embodiment, the invention provides an antibody that selectively binds to a polynucleotide that is a fragment or modified version or is substantially homologous to a polynucleotide that encodes a polypeptide of the invention, or that selectively binds to a molecule that comprises such a polynucleotide.

[0093] In another embodiment, the invention provides an antibody that selectively binds to a cell population of the invention. In a preferred embodiment, the antibody selectively binds to a molecule associated with a cell that is a member of a cell population of the invention; in another preferred embodiment, the cell-associated molecule is a surface antigen.

[0094] Certain antibodies that selectively bind polypeptides of the invention, polynucleotides of the invention, or cell populations and cell-associated molecules of the invention already may be known and/or available for purchase from commercial sources. Antibodies of the invention also may be prepared by any suitable means known in the art. For example, antibodies may be prepared by immunizing an animal host with a marker or an immunogenic fragment thereof (conjugated to a carrier, if necessary). Adjuvants, such as

Freund's adjuvant optionally may be used to increase the immunological response. Sera containing polyclonal antibodies with high affinity for the antigenic determinant can then be isolated from the immunized animal and purified.

[0095] Alternatively, antibody-producing tissue from the immunized host can be harvested and a cellular homogenate prepared from the organ can be fused to cultured cancer cells. Hybrid cells which produce monoclonal antibodies specific for a marker of the invention can be selected. Alternatively, the antibodies of the invention can be produced by chemical synthesis or by recombinant expression. For example, a polynucleotide that encodes the antibody can be used to construct an expression vector for the production of the antibody. The antibodies of the present invention can also be generated using various phage display methods known in the art. Examples of other methods used to identify antibodies include binding assays with random peptide libraries (e.g., phage display), systematic evolution of ligands by exponential enrichment (SELEX) and design methods based on an analysis of the structure of the targeted marker.

[0096] Antibodies that selectively bind markers of the invention can be used, for example, in methods to isolate or detect markers of the invention (e.g., a polypeptide described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, or a cell population described in Table 7 or Table 8) using methods and techniques well-known in the art. In some embodiments, for example, the antibodies are conjugated to a detection molecule or moiety (e.g., a dye, an enzyme) and can be used in ELISA or sandwich assays to detect markers of the invention.

[0097] In another embodiment, antibodies against a polypeptide of the invention, a polynucleotide of the invention, or a cell of a cell population of the invention can be used to assay a tissue sample for such marker. The antibodies can selectively bind any to marker present in the tissue sample sections and allow the localization of the marker in the tissue. Similarly, antibodies labeled with a radioisotope may be used for in vivo imaging or treatment applications. Techniques for conjugating antibodies to therapeutic or imaging agents are well known in the art.

VI. Methods of Diagnosing Rheumatoid Arthritis

[0098] The present invention includes all methods relying on correlations between the polypeptide markers, polynucleotide markers and cell population markers described herein and the presence of RA.

[0099] In one aspect, the invention provides methods for diagnosing RA in a subject. In one embodiment, the invention provides a method for determining whether a subject has RA. These methods comprise obtaining a biological sample from a subject suspected of having RA, or at risk for developing RA, detecting the level or activity of a marker of the invention in the sample, and comparing the result to the level or activity of the marker in a sample obtained from a non-RA subject, or to a standard level or reference range. Typically, the standard level or reference range is obtained by measuring the same marker or markers in a set of non-RA subjects. Measurement of the standard level or reference range need not be made contemporaneously; it may be a historical measurement. Preferably the non-RA subjects are matched to the subject with respect to some attribute(s) (e.g., age and/or sex). Depending upon the difference between the measured level and the standard level or reference range, the subject can be diagnosed as having RA or as not having RA.

[00100] In one embodiment, an increased level or activity of a marker of the invention in a sample obtained from a subject suspected of having RA, or at risk for developing RA, is indicative that the subject has or is at risk for developing RA. Markers appropriate for this embodiment include those that have been identified as increased in samples obtained from RA subjects compared with samples from non-RA subjects (e.g., the polypeptide markers described in Table 1, Table 3 or Table 5 or the cell population markers described in Table 7). Other appropriate markers for this embodiment will be apparent to one of skill in the art in light of the disclosure herein.

[00101] In another embodiment, a decreased level or activity of a marker of the invention in a sample obtained from a subject suspected of having RA, or at risk for developing RA, is indicative that the subject has or is at risk for developing RA. Markers appropriate for this embodiment include those that have been identified as decreased in samples obtained from RA subjects compared with samples from non-RA subjects (e.g., the polypeptide markers described

in Table 2, Table 4 or Table 6 or the cell population markers described in Table 8). Other appropriate markers for this embodiment will be apparent to one of skill in the art in light of the disclosure herein.

[00102] As will be appreciated by one of skill in the art, the methods of the present invention may be used to evaluate fragments of a polypeptide marker listed in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6, as well as molecules that contain the entire polypeptide marker, or at least a significant portion thereof (e.g., measured unique epitope), and modifications of such markers. Accordingly, such fragments, larger molecules and modifications are included within the scope of the invention.

[00103] The methods of the invention may be used to make the diagnosis of RA, independent from other information such as the patient's symptoms, for example, as measured by the American College of Rheumatology (ACR) Criteria (Arnett et al., Arthritis Rheum. 31:315-324 (1988), or the results of other clinical or laboratory tests, such as X-rays of affected joints or previously known markers for RA reported in the literature (e.g., rheumatoid factor). However, the methods of the invention are preferably used in conjunction with such other data points. Similarly, more than one of the markers of the invention may be measured in combination. Measurement of the markers of the invention along with any other markers known in the art, including those not specifically listed herein, falls within the scope of the invention.

[00104] As will be apparent to those of ordinary skill in the art, the method described above is not limited to making an initial diagnosis of RA, but also is applicable to confirming a provisional diagnosis of RA or "ruling out" such a diagnosis.

[00105] What is presently referred to as RA may turn out to be a number of related but distinguishable conditions. For example, RA subjects can be divided into groups based on response to anti-TNF-α therapy. Additional classifications may be made, and these types may be further distinguished into subtypes. Any and all of the various forms of RA are intended to be within the scope of the invention. Indeed, by providing a method for subsetting patients based on marker measurement level, the compositions and methods of the invention may be used to reveal and define various forms of the disease.

[00106] Because a diagnosis is rarely based exclusively on the results of a single test, the methods of the invention may be used to determine whether a subject is more likely than not to have RA, or is more likely to have RA than to have another disease, based on the difference between the measured and standard level or reference range of the marker. Such ranges may be based on other factors such as age and gender. Thus, for example, a patient with a putative diagnosis of RA may be diagnosed as being "more likely" or "less likely" to have RA in light of the information provided by a method of the invention. If a plurality of markers are measured, at least one and up to all of the measured markers must differ, in the appropriate direction, for the subject to be diagnosed as having (or being more likely to have) RA.

[00107] Although markers of the invention were identified in serum and blood, any biological sample may be analyzed for the markers of the invention. Blood, including its constituents such as serum and plasma, and urine represent preferred biological samples for analysis because they are easy samples to obtain. Molecules present in serum are often also present in more easily obtainable fluids such as urine or sputum. Serum and urine also represent preferred biological samples as they are expected to be reflective of the systemic manifestations of the disease. In some embodiments, the level of a marker may be compared to the level of the same or another marker or some other constituent in a different tissue, fluid or biological compartment. Thus, a differential comparison may be made of a marker in synovial fluid and serum, for example. It is also within the scope of the invention to compare the level of a marker with the level of another marker or some other constituent within the same compartment. The marker may be detected in any biological sample obtained from the subject by any suitable method known in the art, see infra.

[00108] As stated above, some of the marker measurement values are higher in samples from RA patients, while others are lower. A significant difference in the appropriate direction in the measured value of one or more of the markers indicates that the patient has (or is more likely to have) RA. If only one marker is measured, then that value must increase or decrease to indicate RA. If more than one marker is measured, then a diagnosis of RA can be indicated by a change in only one marker, all markers, or any number in between. In some preferred embodiments, multiple markers are measured, and a diagnosis of RA is indicated by changes in multiple markers. Measurements can be of (i) a marker of the invention, (ii) a marker of the

invention and another factor known to be associated with RA (e.g., joint tenderness); (iii) a plurality of markers comprising at least one marker of the invention and at least one previously known marker reported in the literature, or (iv) any combination of the foregoing. Furthermore, the amount of change in a marker level may be an indication of the relative likelihood of the presence of the disease.

[00109] The invention also provides methods for determining a subject's risk of developing RA. The method comprises obtaining a biological sample from a subject, detecting the level or activity of a marker of the invention in the sample, and comparing the result to the level or activity of the marker in a sample obtained from a non-RA subject, or to a standard level or reference range, wherein, an increase or decrease of the marker is correlated with the risk of developing RA.

[00110] The invention also provides methods for determining the stage or severity of RA. The method comprises obtaining a biological sample from a subject, detecting the level or activity of a marker in the sample, and comparing the result to the level or activity of the marker of the invention in a sample obtained from a non-RA subject, or to a standard level or reference range, wherein an increase or decrease of the activity or level of the marker is correlated with the age or severity of the disease.

[00111] In an alternative embodiment of the invention, a method is provided for monitoring an RA patient over time to determine whether the disease is progressing. The specific techniques used in implementing this embodiment are similar to those used in the embodiments described above. The method is performed by obtaining a biological sample, such as serum from the subject at a certain time (t_1); measuring the level of at least one of the markers of the invention in the biological sample; and comparing the measured level with the level measured with respect to a biological sample obtained from the subject at an earlier time (t_0). Depending upon the difference between the measured levels, it can be seen whether the marker level has increased, decreased, or remained constant over the interval (t_1-t_0). A further deviation of a marker in the direction indicating RA, or the measurement of additional increased or decreased RA markers, would suggest a progression of the disease during the interval.

Subsequent sample acquisitions and measurements can be performed as many times as desired over a range of times t_2 to t_n.

[00112] The ability to monitor a patient by making serial marker level determinations would represent a valuable clinical tool. Rather than the limited "snapshot" provided by a single evaluation, such monitoring would reveal trends in marker levels over time. In addition to indicating a progression of the disease, tracking the marker levels in a patient could be used to predict exacerbations or indicate the clinical course of the disease. For example, as will be apparent to one of skill in the art, the markers of the invention could be further investigated to distinguish between any or all of the known forms of RA (for example, responders and non-responders to anti-TNF-α therapy) or any later described types or subtypes of the disease. In addition, the sensitivity and specificity of the methods of the invention could be further investigated with respect to distinguishing RA from other autoimmune diseases, other diseases associated with arthritis or to predict relapse and remission.

[00113] Analogously, as described, infra, the markers of the invention can be used to assess the efficacy of a therapeutic intervention in a subject. The same approach described above would be used, except a suitable treatment would be started, or an ongoing treatment would be changed, before the second measurement (i.e., after t_0 and before t_1). The treatment can be any therapeutic intervention, such as drug administration, dietary restriction or surgery, and can follow any suitable schedule over any time period. The measurements before and after could then be compared to determine whether or not the treatment had an effect effective. As will be appreciated by one of skill in the art, the determination may be confounded by other superimposed processes (e.g., an exacerbation of the disease during the same period).

[00114] It is to be understood that any correlations between biological sample measurements of the markers of the invention and RA, as used for diagnosis of the disease or evaluating drug effect, are within the scope of the invention.

VII. Methods for Measuring

[00115] In the methods of the invention, levels and activity of polypeptides of the invention, polynucleotides of the invention, or cell populations of the invention are measured (or

detected) using conventional techniques. The measurement may be quantitative or qualitative. The measurement may be absolute or relative. It should be noted that while one technique may be used to identify the marker, in practice, a different technique may be used to measure the level or activity of the marker. A wide variety of techniques are available, including without limitation mass spectrometry, chromatographic separations, 2-D gel separations, binding assays (e.g., immunoassays), hybridization assays, enzyme assays and competitive inhibition assays, immunofluorescence and cytometry. Any effective method in the art for measuring the level or activity of a polypeptide, polynucleotide or cell population marker of the invention is included in the invention. It is within the ability of one of ordinary skill in the art to determine which method would be most appropriate for measuring a specific marker. Thus, for example, a robust ELISA assay may be best suited for use in a physician's office while a measurement requiring more sophisticated instrumentation may be best suited for use in a clinical laboratory. Regardless of the method selected, it is important that the measurements be reproducible.

[00116] Mass spectrometry, which allows direct measurement of analytes with high sensitivity and reproducibility, advantageously can be used to measure polypeptide markers of the invention. A number of mass spectrometric methods are available and could be used to accomplish the measurement. Electrospray ionization (ESI), for example, allows quantification of differences in relative concentration of various species in one sample against another; absolute quantification is possible by normalization techniques (e.g., using an internal standard). Matrix-assisted laser desorption ionization (MALDI) or the related SELDI® technology (Ciphergen, Inc.) also could be used to make a determination of whether a marker was present, and the relative or absolute level of the marker. Moreover, mass spectrometers that allow time-of-flight (TOF) measurements have high accuracy and resolution and are able to measure low abundant species, even in complex matrices like serum or synovial fluid.

[00117] For polypeptide markers, quantification can be based on derivatization in combination with isotopic labeling, referred to as isotope coded affinity tags ("ICAT"). In this and other related methods, a specific amino acid in two samples is differentially and isotopically labeled and subsequently separated from peptide background by solid phase capture, wash and release. The intensities of the molecules from the two sources with different isotopic labels can then be accurately quantified with respect to one another.

[00118] In addition, one- and two-dimensional gels have been used to separate polypeptides and quantify gel spots by silver staining, fluorescence or radioactive labeling. These differently stained spots have been detected using mass spectrometry, and identified by tandem mass spectrometry techniques.

[00119] In preferred embodiments, the polypeptide markers are measured using mass spectrometry in connection with a separation technology, such as liquid chromatography-mass spectrometry or gas chromatography-mass spectrometry. It is particularly preferable to couple reverse-phase liquid chromatography to high resolution, high mass accuracy ESI time-of-flight (TOF) mass spectroscopy. This allows spectral intensity measurement of a large number of biomolecules from a relatively small amount of any complex biological material without sacrificing sensitivity or throughput. Analyzing a sample by this method allows the marker (characterized by, for example, the M+H value, or the retention time and mass-to-charge ratio within the given experimental platform) to be determined and quantified.

[00120] As will be appreciated by one of skill in the art, many other separation technologies may be used in connection with mass spectrometry. For example, a vast array of separation columns are commercially available. In addition, separations may be performed using custom chromatographic surfaces (e.g., a bead on which a marker specific reagent has been immobilized). Molecules retained on the media subsequently may be eluted for analysis by mass spectrometry.

[00121] Analysis by liquid chromatography-mass spectrometry produces a mass intensity spectrum, the peaks of which represent various components of the sample, each component having a characteristic mass-to-charge ratio (m/z) and retention time (R.T.) within the given experimental platform. Each polypeptide will have a characteristic M+H value. As one of skill in the art will recognize, there may not be a one-to-one correspondence between components (each with a characteristic m/z and R.T. within the given experimental platform) and the polypeptides having a characteristic M+H value (i.e., the former typically will outnumber the latter). The presence of a peak with the m/z and RT of a marker indicates that the marker is present. The peak representing a marker may be compared to a corresponding peak from another spectrum (e.g., from a control sample) to obtain a relative measurement. Any normalization

technique in the art (e.g., an internal standard) may be used when a quantitative measurement is desired. In addition, deconvoluting software is available to separate overlapping peaks. The retention time depends to some degree on the conditions employed in performing the liquid chromatography separation. The preferred conditions, and the conditions used to obtain the retention times that appear in the Tables, are set forth in Example 2. The various polypeptides of the invention have a characteristic M+H value.

[00122] The better the mass assignment, the more accurate is the detection and measurement of the marker level in the sample. Thus, the mass spectrometer selected for this purpose preferably provides high mass accuracy and high mass resolution. The mass accuracy of a well-calibrated Micromass TOF instrument, for example, is reported to be approximately 2 mDa, with resolution $m/\Delta m$ exceeding 5000.

[00123] In other preferred embodiments, the level of the polypeptide markers may be determined using a standard immunoassay, such as a sandwich ELISA using matched antibody pairs and chemiluminescent detection. Commercially available or custom monoclonal or polyclonal antibodies are typically used. However, the assay can be adapted for use with other reagents that selectively bind to the marker. Standard protocols and data analysis are used to determine the marker concentrations from the assay data.

[00124] A number of the assays discussed above employ an antibody that selectively binds to the marker. An antibody may be identified and produced by any method accepted in the art, as discussed, supra.

[00125] The polypeptide markers of the invention also may be measured using a number of chemical derivatization or reaction techniques known in the art. Reagents for use in such techniques are known in the art, and are commercially available for certain classes of target molecules.

[00126] Finally, the chromatographic separation techniques described above also may be coupled to an analytical technique other than mass spectrometry such as fluorescence detection of tagged molecules, NMR, capillary UV, evaporative light scattering or electrochemical detection.

[00127] The intracellular levels of polypeptide markers can also be measured. Typical methodologies include protein extraction from a cell or tissue sample, followed by hybridization of a labeled probe (e.g., an antibody) specific for the target protein to the protein sample, and detection of the probe. The label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Detection of specific polypeptides may also be assessed by gel electrophoresis or column chromatography, among many other techniques well known to those skilled in the art.

[00128] Measurement of the level of a polynucleotide marker may be made by any method known in the art. See, e.g., Sambrook et al., supra; Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons (1992).

[00129] Typical methodologies for RNA detection include RNA extraction from a cell or tissue sample, followed by hybridization of a labeled probe (e.g., a complementary polynucleotide) specific for the target RNA to the extracted RNA, and detection of the probe (e.g., Northern blotting). Detection of specific polynucleotides may also be assessed by gel electrophoresis, column chromatography, direct sequencing, or quantitative PCR, among many other techniques well known to those skilled in the art.

[00130] Detection of the presence or number of copies of all or a part of a polypeptide marker gene or polynucleotide of the invention may be performed using any method known in the art. Typically, it is convenient to assess the presence and/or quantity of a DNA or cDNA by Southern analysis, in which total DNA from a cell or tissue sample is extracted, is hybridized with a labeled probe (e.g., a complementary DNA molecule), and the probe is detected. The label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Other useful methods of DNA detection and/or quantification include direct sequencing, gel electrophoresis, column chromatography, and quantitative PCR, as is known by one skilled in the art.

[00131] Polynucleotide similarity can be evaluated by hybridization between single stranded nucleic acids with complementary or partially complementary sequences. Such experiments are well known in the art.

[00132] Cell populations of the invention may be measured and characterized by any method or technique accepted in the art. Flow cytometry, for example, is a widely used means for analyzing the physical and chemical properties of cell populations. Monoclonal antibodies against specific cell-surface or intracellular antigens, conjugated to fluorescent dyes, can be used as probes to detect expression of cellular antigens. After staining a sample with one or more fluorescent probes (either singly or in combination) the cells are conducted by the rapidly flowing stream, one at a time, though a focused laser beam. Information about the cell (e.g., its type, structure, size) can be determined from the fluorescent signal, and the manner in which the cell interacts with and scatters the light from the laser beam. The resulting data is typically compiled in a computer file for subsequent analysis. Flow cytometry also can be used to physically separate cells with particular characteristics ("cell sorting").

[00133] Alternatively, cell populations of the invention may be analyzed using microvolume laser scanning cytometry (MLSC). In MLSC, as with flow cytometry, fluorophore-labeled antibodies specific for cell surface antigens are used to identify, characterize, and enumerate specific leukocyte populations. In a preferred embodiment, the SurroScan™ MLSC is used to classify and quantify cell populations. See Dietz et al., U.S. Patent No. 6,603,537 (issued Aug. 5, 2003); Dietz et al., U.S. Patent No. 6,687,395 (issued Feb. 3, 2004), Walton et al., supra. The staining reaction can be done with essentially any cell suspension, including whole blood, and assays can be executed in homogeneous mode. Typically, quantitative dilution of the blood-antibody mixture is usually sufficient sample preparation eliminating the need to wash away the reagent, significantly reducing the time needed for sample preparation.

[00134] After staining, the cell-antibody mixtures are loaded into optical-quality capillary arrays. The leukocytes of interest distribute throughout the capillary and, in whole blood assays, float to the top of the red cell hematocrit. In order to operate with whole blood, fluorophores that can be excited in the red region (> 600 nm) of the spectrum with a HeNe laser, such as Cy5, Cy5.5 and Cy7-APC, are preferred. White blood cells isolated following ficoll or erythrocyte-lysis can also be routinely analyzed.

[00135] Each capillary in the array is analyzed with the laser-based fluorescence-imaging instrument. In contrast to flow cytometry, the laser scans over stationary cells rather than cells flowing past the laser. A small cylindrical laser spot is scanned across the capillary in one direction while the capillary is translated relative to the optical system in a second direction. Typically three antibody reagents, each with a different fluorescent tag and each detected in a different channel, are used per assay. The capillary is imaged and fluorescent events detected. This is in contrast to flow cytometry where light scatter rather than fluorescence is usually the trigger parameter.

[00136] Peaks corresponding to antibody-labeled cells are identified with image processing software that produces a list-mode data file with parameters for every detected cell event. Norton et al., supra. Unlabeled cells i.e., erythrocytes and leukocytes not expressing the target antibodies, are not identified. Intensity data is compensated for spectral overlap, so the resultant values are proportional to the amount of dye-antibody reagent on each cell. The volume of the scan is precisely defined enabling absolute cell counts (cells per μL of blood) to be determined.

[00137] Assay panels may be devised to identify and enumerate hundreds of different cell types and cell-associated molecules that are relevant to immune, inflammatory and metabolic processes. In a preferred embodiment, each reagent cocktail typically contains one or two antibodies to the major cell populations - neutrophils, eosinophils, monocytes T-cells, B-cells, NK-cells, and platelets – and one or two antibodies to subsetting antigens which may indicate the functional state, activation state or adhesion characteristics of the population.

VIII. Method of Treatment

[00138] This invention also provides method for treating RA, as well as other diseases or conditions, by providing a therapeutic agent to a subject that increases or decreases the level or activity of at least one polypeptide of the invention, polynucleotide of the invention, or cell population of the invention.

[00139] In one embodiment, the method comprises administering a therapeutic agent to a subject that increases the level or activity of at least one polypeptide of the invention,

polynucleotide of the invention or cell population of the invention that is decreased in samples obtained from RA subjects compared to samples obtained from non-RA subjects or to a standard level or reference range.

[00140] In another embodiment, the method comprises administering a therapeutic agent to a subject that decreases the level of at least one polypeptide of the invention, polynucleotide of the invention or cell population of the invention that is increased in samples obtained from RA subjects compared to samples obtained from non-RA subjects or to a standard level or reference range.

[00141] In another embodiment, the method further comprises first obtaining a sample from an RA subject, determining the presence, level or activity of at least one marker of the invention in the sample compared to samples obtained from a non-RA subject or to a standard value or a reference range. If the marker is increased in the sample obtained from the RA subject, a therapeutic agent that decreases the level of the marker is administered to the patient. If the marker is decreased in the sample obtained from the RA subject, a therapeutic agent that increases the level of the marker is administered to the subject.

[00142] Therapeutic agents include but are not limited to polypeptide markers, polynucleotide markers, molecules comprising polypeptide markers or polynucleotide markers, antibodies specific for polypeptides of the invention, polynucleotides of the invention, or cell populations of the invention, modulators of the level or activity of a polypeptide of the invention, polynucleotide of the invention or cell population marker of the invention or compositions comprising one or more of the foregoing.

[00143] Generally, the therapeutic agents used in the invention are administered to the subject in an effective amount. An "effective amount" is typically the amount that is sufficient to obtain beneficial or desired clinical results. The effective amount is generally determined by a physician with respect to a specific patient and is within the skill of one in the art. Factors that may be taken into account in determining an effective amount include those relating to the condition being treated (e.g., type, stage, severity) as well as those relating to the subject (e.g., age, sex, weight).

[00144] The level or activity of a polypeptide marker may be increased or decreased by any suitable technique or method known in the art. The level of a polypeptide marker may be increased by providing the polypeptide marker to a subject. Alternatively, the level of a polypeptide marker may be increased by providing a polynucleotide that encodes the polypeptide marker (e.g., gene therapy). For those polypeptide markers with enzymatic activity, compounds or molecules known to increase that activity may be provided to the subject.

[00145] The level of a polypeptide marker may be decreased by providing antibodies specific for the polypeptide marker to the subject. Alternatively, the level of a polypeptide marker may be decreased by providing a polynucleotide that is "anti-sense" to the polynucleotide that encodes the polypeptide marker, or that encodes dysfunctional proteins. For those polypeptide markers with enzymatic activity, compounds or molecules known to decrease that activity (e.g., inhibitor or antagonist).

[00146] Polynucleotides of the invention may also be used to specifically suppress gene expression by methods such as RNA interference (RNAi), which may also include cosuppression and quelling. This and other techniques of gene suppression are well known in the art. A review of this technique is found in Marx, Science 288:1370-1372 (2000). Specifically, polynucleotides of the invention are useful for generating gene constructs for silencing specific genes. Polynucleotides of the invention may be used to generate genetic constructs that encode a single self-complementary RNA sequence specific for one or more genes of interest. Genetic constructs and/or gene-specific self-complementary RNA sequences may be delivered by any conventional method known in the art. Within genetic constructs, sense and antisense sequences flank an intron sequence arranged in proper splicing orientation making use of donor and acceptor splicing sites. Alternative methods may employ spacer sequences of various lengths rather than discrete intron sequences to create an operable and efficient construct. During post-transcriptional processing of the gene construct product, intron sequences are spliced-out, allowing sense and antisense sequences, as well as splice junction sequences, to bind forming double-stranded RNA. Select ribonucleases bind to and cleave the double-stranded RNA, thereby initiating the cascade of events leading to degradation of specific mRNA gene sequences, and silencing specific genes. Alternatively, rather than using a gene construct to express the self-complementary RNA sequences, the gene-specific double-stranded RNA segments are delivered

to one or more targeted areas to be internalized into the cell cytoplasm to exert a gene silencing effect. Using this cellular pathway of gene suppression, gene function may be studied and high-throughput screening of sequences may be employed to discover sequences affecting gene expression.

[00147] The level of a cell population may be increased or decreased by any suitable technique or method known in the art. The level of a cell population may be increased in a sample, for example, by providing an appropriate chemoattractant. Chemokines, for example, have been shown to control the migratory behavior of several cell types, including lymphocytes. Conversely, the level of a cell population may be decreased by providing to the subject antibodies specific for the cell population.

[00148] The therapeutic agents described herein may be administered alone or in combination with another therapeutic compound, or other form of treatment. The compounds may be administered to the subjects in any suitable manner known in the art (e.g., orally, topically, subcutaneously, intradermally, intramuscularly, intravenously, intra-arterially, intrathecally). Therapeutic agents of the invention may be combined with an excipient and formulated as tablets or capsules for oral administration. Polypeptides may be formulated for parenteral administeration to avoid denaturation by stomach acids. For polynucleotides, vectors may be constructed for administration to the subject by a virus or other carrier. In a typical embodiment, cDNA is delivered to target cells (e.g., bone marrow cells) that are later reintroduced into the subject for expression of the encoded protein.

[00149] The therapeutic agents of the invention can be administered by any suitable means, including, for example, parenteral, intravenous, topical, oral or local administration, such as intradermally, by aerosol, or by injection. A therapeutic composition can be administered in a variety of unit dosage forms depending upon the method of administration. For example, unit dosage forms suitable for oral administration of subject include powder, tablets, pills and capsules. For particular modes of delivery, a therapeutic composition of the invention can be formulated in an excipient of the invention. A therapeutic reagent of the invention can be administered to any subject, including a human, a non-human mammal or other non-human animal.

[00150] As one of skill in the art will appreciate, the particular mode of administration will depend on the condition to be treated. It is contemplated that administration of the agents of the invention may be via any suitable method known in the art.

[00151] Antibodies targeting cell populations of the invention advantageously may be administered by intravenous, interperitoneal, or subcutaneous injection, including administration to veins or the lymphatic system, or directly into the joint space.

[00152] In a further embodiment, the therapeutic agents of the invention are useful for gene therapy or gene delivery. As used herein, the phrases "gene therapy" or “gene delivery” refer to the transfer of genetic material (e.g., DNA or RNA) of interest into a host to treat or prevent a genetic or acquired disease or condition. The genetic material of interest encodes a product (e.g., a protein polypeptide, peptide or functional RNA) whose production in vivo is desired. For example, the genetic material of interest can encode a hormone, receptor, enzyme or polypeptide of therapeutic value. In a specific embodiment, the subject invention utilizes a class of lipid compounds for use in non-viral gene therapy which can complex with nucleic acids as described in Hughes, et al., U.S. Patent No. 6,169,078 (issued Jan. 2, 2001), incorporated by reference herein in its entirety. These therapeutic compounds effectively complex with DNA and facilitate the transfer of DNA through a cell membrane into the intracellular space of a cell to be transformed with heterologous DNA. Furthermore, these lipid molecules facilitate the release of heterologous DNA in the cell cytoplasm thereby increasing gene transfection during gene therapy in a human or animal.

IX. Therapeutic Compositions

[00153] Another aspect of the invention provides compositions comprising a polypeptide of the invention, a polynucleotide of the invention, an antibody against a polypeptide of the invention, polynucleotide of the invention, or cell population of the invention, an inhibitor of a polypeptide of the invention, polynucleotide of the invention, or cell population of the invention, or other molecule that can increase or decrease the level or activity of a polypeptide of the invention, polynucleotide of the invention or cell population of the invention. Such compositions may be pharmaceutical compositions formulated for use as a therapeutic.

[00154] In one embodiment, the invention provides a composition that comprises a polypeptide of the invention, including without limitation a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5 or Table 6 or any of the other polypeptide markers of the invention described herein.

[00155] In one embodiment, the invention provides a composition that comprises a polynucleotide of the invention of the invention, including without limitation a polynucleotide that encodes a polypeptide marker described in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6 or any of the other nucleotides of the invention described herein.

[00156] In another embodiment, the invention provides a composition that comprises an antibody that selectively binds to a polypeptide of the invention, a polynucleotide of the invention or a cell population of the invention, or a molecule that comprises such an antibody.

[00157] In another embodiment, the invention provides a composition that comprises a modulator of the level or activity of a polypeptide of the invention, a polynucleotide of the invention, or cell population of the invention, or a molecule that comprises such a modulator. In one embodiment, the modulator is an inhibitor of a polypeptide of the invention. In another embodiment, the modulator is an antisense polynucleotide that is complementary to a polynucleotide that encodes a polypeptide of the invention.

[00158] Such compositions may be pharmaceutical compositions. Typically, a pharmaceutical composition comprises a therapeutically effective amount of an active agent and is formulated with a suitable excipient or carrier.

[00159] Generally, the therapeutic agents used in the invention are administered to the subject in an effective amount. Generally, an effective amount is an amount effective to either (1) reduce the symptoms of the disease sought to be treated or (2) induce a pharmacological change relevant to treating the disease sought to be treated. For RA, an effective amount includes an amount effective to: improve the DAS28 score, improve the American College of Rheumatology (ACR) functional scores, decrease tender and swollen joint counts, decrease duration of morning stiffness, and reduce any other objective or subjective indicia of the disease. Therapeutically effective amounts of the therapeutic agents will depend, in part, on the condition,

type and location of the disease, the size and condition of the patient, as well as other factors readily known to those skilled in the art. The dosages can be given as a single dose, or as several doses, for example, divided over the course of several weeks.

[00160] The pharmaceutical compositions of the invention can be prepared in any suitable manner known in the pharmaceutical art. The carrier or excipient may be a solid, semisolid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art and include, but are not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The pharmaceutical compositions may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, powders, syrups, and the like. As used herein, the term "pharmaceutical carrier" may encompass one or more excipients. Suitable pharmaceutical carriers and formulation techniques are found in standard texts, such as Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania.

[00161] One embodiment of the invention is a controlled release formulation that is capable of slowly releasing a composition of the invention into an animal. As used herein, a controlled release formulation comprises a composition of the invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the invention include liquids that, upon administration to an animal, form a solid or a gel in situ. Preferred controlled release formulations are biodegradable (i.e., bioerodible).

X. Methods for Screening Candidate Compounds

[00162] In another aspect, the invention provides methods for screening candidate compounds for use as therapeutic agents. In one embodiment, the method comprises screening candidate compounds for those that bind to a polypeptide of the invention, a polynucleotide of the invention, or a cell population of the invention. Candidate compounds that bind to markers can be identified using any suitable method or technique known in the art.

[00163] In one embodiment, a candidate compound or a control is contacted with a marker of the invention and the ability of the candidate compound to form stable complexes with the marker is determined (e.g., flow cytometry, immunoprecipitation). The candidate compound, the marker, or an antibody that selectively binds either may be labeled to facilitate detection. The candidate molecule or marker may be immobilized on a solid support (e.g., a bead).

[00164] In another embodiment, cells expressing a polypeptide marker are contacted with a candidate compound or a control and the ability of the candidate compound to form stable complexes with the cells is determined. The candidate compound or the marker may be labeled to facilitate detection.

[00165] In another embodiment, the method comprises screening candidate compounds for those that have a stimulatory or inhibitory effect on the activity of a marker of the invention comprising comparing the activity of the marker in the presence of the candidate molecule with the activity of the marker in the absence of the candidate molecule (e.g., in the presence of a control).

[00166] In another embodiment, the method comprises screening candidate drugs in a clinical trial to determine whether a candidate drug is effective in treating RA. At time t_o, a biological sample is obtained from each subject in population of subjects diagnosed with RA. Next, assays are performed on each subject's sample to measure levels of a marker. In some embodiments, only a single marker is monitored, while in other embodiments, a combination of markers, up to the total number of factors, is monitored. Next, a predetermined dose of a candidate drug is administered to a portion or sub-population of the same subject population. Drug administration can follow any suitable schedule over any time period. In some cases, varying doses are administered to different subjects within the sub-population, or the drug is administered by different routes. At time t_1, after drug administration, a biological sample is acquired from the sub-population and the same assays are performed on the biological samples as were previously performed to obtain measurement values. As before, subsequent sample acquisitions and measurements can be performed as many times as desired over a range of times t_2 to t_n. In such a study, a different sub-population of the subject population serves as a control group, to which a placebo is administered. The same procedure is then followed for the control

group: obtaining the biological sample, processing the sample, and measuring the markers to obtain a measurement chart.

[00167] Specific doses and delivery routes can also be examined. The method is performed by administering the candidate drug at specified dose or delivery routes to subjects with RA; obtaining biological samples, such as serum, from the subjects; measuring the level of at least one of the markers in each of the biological samples; and, comparing the measured level for each sample with other samples and/or a standard level or reference range. Typically, the standard level or reference range is obtained by measuring the same marker or markers in the subject before drug administration. Depending upon the difference between the measured and standard levels, the drug can be considered to have an effect on RA. If multiple markers are measured, at least one and up to all of the markers must change, in the expected direction, for the drug to be considered effective. Preferably, multiple markers must change for the drug to be considered effective, and preferably, such change is statistically significant.

[00168] As will be apparent to those of ordinary skill in the art, the above description is not limited to a candidate drug, but is applicable to determining whether any therapeutic intervention is effective in treating RA.

[00169] In a typical embodiment, a subject population having RA is selected for the study. The population is typically selected using standard protocols for selecting clinical trial subjects. For example, the subjects are generally healthy, are not taking other medication, and are evenly distributed in age and sex. The subject population can also be divided into multiple groups; for example, different sub-populations may be suffering from different types or different degrees of the disorder to which the candidate drug is addressed.

[00170] In general, a number of statistical considerations must be made in designing the trial to ensure that statistically significant changes in marker measurements can be detected following drug administration. The amount of change in a marker depends upon a number of factors, including strength of the drug, dose of the drug, and treatment schedule. It will be apparent to one skilled in statistics how to determine appropriate subject population sizes. Preferably, the study is designed to detect relatively small effect sizes.

[00171] The subjects optionally may be "washed out" from any previous drug use for a suitable period of time. Washout removes effects of any previous medications so that an accurate baseline measurement can be taken. At time t_o, a biological sample is obtained from each subject in the population. Preferably, the sample is blood, but other biological fluids may be used (e.g., urine). Next, an assay or variety of assays are performed on each subject's sample to measure levels of particular markers of the invention. The assays can use conventional methods and reagents, as described above. If the sample is blood, then the assays typically are performed on either serum or plasma. For other fluids, additional sample preparation steps are included as necessary before the assays are performed. The assays measure values of at least one of the markers of the invention. In some embodiments, only a single marker is monitored, while in other embodiments, a combination of factors, up to the total number of markers, is monitored. The markers may also be monitored in conjunction with other measurements and factors associated with RA (e.g., joint tenderness). The number of markers whose values are measured depends upon, for example, the availability of assay reagents, biological fluid, and other resources.

[00172] Next, a predetermined dose of a candidate drug is administered to a portion or sub-population of the same subject population. Drug administration can follow any suitable schedule over any time period, and the sub-population can include some or all of the subjects in the population. In some cases, varying doses are administered to different subjects within the sub-population, or the drug is administered by different routes. Suitable doses and administration routes depend upon specific characteristics of the drug. At time t_1, after drug administration, another biological sample (the "t_1 sample") is acquired from the sub-population. Typically, the sample is the same type of sample and processed in the same manner (for example, blood) as the sample acquired from the subject population before drug administration (the "t_o sample"). The same assays are performed on the t_1 sample as on the t_o sample to obtain measurement values. Subsequent sample acquisitions and measurements can be performed as many times as desired over a range of times t_2 to t_n.

[00173] Typically, a different sub-population of the subject population is used as a control group, to which a placebo is administered. The same procedure is then followed for the control group: obtaining the biological sample, processing the sample, and measuring the markers to

obtain measurement values. Additionally, different drugs can be administered to any number of different sub-populations to compare the effects of the multiple drugs. As will be apparent to those of ordinary skill in the art, the above description is a highly simplified description of a method involving a clinical trial. Clinical trials have many more procedural requirements, and it is to be understood that the method is typically implemented following all such requirements.

[00174] Paired measurements of the various markers are thus determined for each subject. The different measurement values are compared and analyzed to determine whether the markers changed in the expected direction for the drug group but not for the placebo group, indicating that the candidate drug is effective in treating RA. In preferred embodiments, such change is statistically significant. The measurement values at time t_1 for the group that received the candidate drug are compared with standard measurement values, preferably the measured values before the drug was given to the group, i.e., at time t_0. Typically, the comparison takes the form of statistical analysis of the measured values of the entire population before and after administration of the drug or placebo. Any conventional statistical method can be used to determine whether the changes in marker values are statistically significant. For example, paired comparisons can be made for each marker using either a parametric paired t-test or a non-parametric sign or sign rank test, depending upon the distribution of the data.

[00175] In addition, tests should be performed to ensure that statistically significant changes found in the drug group are not also found in the placebo group. Without such tests, it cannot be determined whether the observed changes occur in all patients and are therefore not a result of candidate drug administration.

[00176] As discussed, supra, some of the marker measurement values are higher in samples from RA patients, while others are lower. The nonadjusted p-values shown were obtained by univariate analysis. A significant change in the appropriate direction in the measured value of one or more of the markers indicates that the drug is effective. If only one marker is measured, then that value must increase or decrease to indicate drug efficacy. If more than one marker is measured, then drug efficacy can be indicated by change in only one marker, all markers, or any number in between. In some embodiments, multiple markers are measured, and drug efficacy is indicated by changes in multiple markers. Measurements can be of both

markers of the invention and other measurements and factors associated with RA (e.g., measurement of previously known markers reported in the literature). Furthermore, the amount of change in a marker level may be an indication of the relatively efficacy of the drug.

[00177] In addition to determining whether a particular drug is effective in treating RA, markers of the invention can also be used to examine dose effects of a candidate drug. There are a number of different ways that varying doses can be examined. For example, different doses of a drug can be administered to different subject populations, and measurements corresponding to each dose analyzed to determine if the differences in the markers before and after drug administration are significant. In this way, a minimal dose required to effect a change can be estimated. In addition, results from different doses can be compared with each other to determine how each marker behaves as a function of dose.

[00178] Analogously, administration routes of a particular drug can be examined. The drug can be administered differently to different subject populations, and measurements corresponding to each administration route analyzed to determined if the differences in the markers before and after drug administration are significant. Results from the different routes can also be compared with each other directly.

XI. Kits

[00179] In another aspect, the invention provides a kit for detecting a polypeptide of the invention, a polynucleotide of the invention or a cell population of the invention.

[00180] In another aspect, the invention provides a kit for diagnosing RA in a patient by detecting at least one polypeptide of the invention, polynucleotide of the invention or cell population of the invention in a biological sample from the subject. In one embodiment, the kit is for monitoring progression of the disease. In another embodiment, the kit is for assessing response to therapy.

[00181] In another aspect, the invention provides a kit for screening candidate compounds by detecting stable complexes between the candidate compound and a polynucleotide of the invention, polynucleotide of the invention or cell population of the invention.

[00182] The kits of the invention may comprise one or more of the following: an antibody, wherein the antibody selectively binds to a polypeptide of the invention, polynucleotide of the invention or cell population of the invention, a labeled binding partner to the antibody (e.g., a "secondary antibody"), a solid phase upon which is immobilized the antibody or its binding partner, a polynucleotide probe that can hybridize to a polynucleotide marker, pairs of primers that under appropriate reaction conditions can prime amplification of at least a portion of a polynucleotide marker or a polynucleotide encoding a polypeptide marker (e.g., by PCR), instructions on how to use the kit, a container for a collected sample, or a label or insert indicating regulatory approval for diagnostic or therapeutic use.

[00183] In developing such kits, it is within the competence of one of ordinary skill in the art to perform validation studies that would use an optimal analytical platform for each marker. For a given marker, this may be an immunoassay, flow cytometer assay or mass spectrometry assay. Kit development may require specific antibody development, evaluation of the influence (if any) of matrix constituent ("matrix effects"), and assay performance specifications.

EXAMPLES

Example 1 – Clinical Study

[00184] The Institutional Review Board (IRB) approved protocol includes collection of samples from subjects with established RA (RA subjects) and non-RA subjects, matched for age gender and co-morbidities.

[00185] For the cell population analysis, RA subjects included individuals with a range of disease activity from remission to severe based on Disease Activity Scores. Specifically, the DAS28, a composite index of swollen and tender joints, erythrocyte sedimentation rate and general health, was used. van der Heijde et al., Ann. Rheum. Dis. 49:919–20 (1990); Prevoo et al., Arthritis Rheum. 38:44-8 (1995). Subject scores ranged from < 2 to 7.7 (median 2.9) and ACR functional scores ranged from 1 to 4. Two cross sectional studies, with different panels of cellular assays compared 95 RA subjects and 30 non-RA subjects and 77 RA subjects and 48 non-RA subjects, respectivley.

[00186] For the mass spectrometry analysis, RA subjects included individuals with moderate to severe disease activity, with DAS28 scores ranging from 3.3 to 7.7 (median 5.2) and ACR functional scores of 3 or 4. The cross sectional study compared 20 RA subjects and 20 healthy subjects.

[00187] In both cases, serum samples were collected from RA and non-RA subjects in accordance with a clinical protocol and informed consent that were approved by an institutional review board (IRB) and with procedures that adhere to Good Clinical Practice.

Example 2 – Mass Spectrometry Analysis

[00188] A high molecular weight fraction ("serum proteome") was separated from the serum samples using a 5-kDa molecular weight cut-off spin filter (Millipore Corp., Bedford, MA). The serum proteome was diluted with PBS buffer (pH 6.0). To increase the effective dynamic range of the measurements, the two most abundant proteins (human serum albumin and IgG) were substantially depleted by an affinity resin (ProMetic Biosciences, Cambridge, UK). The remaining proteins were denatured using guanidine hydrochloride, disulfide bonds were reduced using dithioreitol, and sulfhydryl groups were carboxymethylated using iodoacetic acid/NaOH. The denaturant and reduction-alkylation reagents were removed by buffer exchange. After digestion of the proteins using modified Trypsin (Promega Corp., Madison, WI), the mixture was lyophilized to a powder, dissolved in formic acid, desalted, dried again, and redissolved in 0.1% formic acid for injection onto the liquid chromatography-mass spectrometer.

[00189] The tryptic peptides were profiled by liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) on a high-resolution time-of-flight (TOF) instrument. For LC separation, an online column (PicoTip, New Objective) was packed with C18 reverse-phase (RP) material. Peptides retained on the RP column were eluted with increasing concentration of acetonitrile (ACN). A 100 minute gradient of H_2O/AcN was the basis of elution , going to 40% acetonitrile. The eluate from the column flowed into the ESI-TOF MS (Micromass LCT™, Waters Corp., Milford, MA). Individual molecules were tracked across samples and their differential expression determined.

[00190] A binary HP 1100 series HPLC was directly coupled to a MicroMass (Manchester, UK) LCT™ EST-TOF mass spectrometer equipped with a nanospray source (New Objective, Woburn, MA) for serum profiling or a ThermoFinnigan (San Jose, CA) LCQ DECA™ ESI ion-trap mass spectrometer for peptide identification. Details of the system set-up are described elsewhere. Wang et al., supra. Mass peaks were analyzed with MassView™ software (SurroMed, Inc., Menlo Park, CA), which tracks peaks and performs normalization to enable quantitative comparisons across multiple samples. Wang et al., supra; Hastings et al. Rapid Commun. Mass Spectrom., 16:462-7 (2002).

Example 3 – Cell Population Analysis

[00191] Cellular assays were conducted on the SurroScan™ microvolume laser scanning cytometer (MLSC) using Flex32™ capillary arrays (SurroMed Inc., Menlo Park, CA). Walton et al., supra. The SurroScan system is based in part on the Imagn2000™ MLSC (Becton Dickinson, San Jose, CA). Dietz et al., Cytometry, 23177-86 (1996). However, in the SurroScan system (i) four colors can be analyzed instead of two, (ii) capillary arrays are used to enable many more assays and (iii) software enables streamlined data processing and connection to the database.

[00192] Monoclonal antibodies and fluorescent tags were obtained from commercial vendors (BD Biosciences, San Jose, CA, including BD PharMingen, San Jose, CA; Beckman Coulter, Miami, FL; Serrotec, Raleigh, NC; and eBiosciences, San Diego, CA). Three different fluorophores were used as direct conjugates to the antibodies: Cy5, Cy5.5, and Cy7-APC. Mujumdar et al. Bioconjug. Chem. 4:105-11 (1993); Beavis & Pennline, Cytometry 24:390-394 (1996); Roederer et al., Cytometry, 24:191-7 (1996). Antibody-dye reagents were titrated to determine the appropriate concentration and combined into pre-made cocktails.

[00193] Images were converted to flow cytometry standard format with in-house software and analyzed with FlowJo™ cytometry analysis software customized for SurroMed (Tree Star, Inc., San Carlos, CA). Norton et al., supra. Fluorescence intensities were compensated for spectral overlap of the dyes so values would be proportional to antigen density. For the clinical study, list mode data is uploaded into an Oracle database and analyzed with in-house software using standard gates developed with the FlowJo and uploaded into the database.

[00194] About 800 cellular variables were analyzed, including cell counts, cell ratios and intensities. Some of these unique combinations were not independent and may represent the same or overlapping biological cell populations. For the major cell populations (neutrophils, eosinophils, monocytes, total T-cells, CD4 T-cells, CD8 T-cells, B-cells and NK cells) that were measured by an identical two-antigen combination (each with a different third antigen) in multiple assays, appropriate averages were calculated and used as a single variable for comparative statistics. Many of the cell populations in Table 7 and Table 8 are designated by the antigens used to define them where p=positive, n=negative, pn=dull, t=total in the assay. Thus, "CD3p" indicates a CD3 positive cell).

Whole blood assays results for T cell subsets; cell events can be displayed in histograms or dot plots based on the level of antigen expression. CD4 and CD8 T cells can be divided into naïve and memory T cell subsets. Four subsets can be identified and related to specific functional states: naïve ($CD45RA^+$, $CD62L^+$), central memory ($CD45RA^-$, $CD62L^+$), effector memory cells ($CD45RA^-$, $CD62L^-$) and terminal effector memory ($CD45RA^+$, $CD62L^-$) according to one scheme for CD8 T cells. Hamann et al., Intl. Immunol., 11:1027-1033 (1999); Sallusto et al., Nature, 401:708-712 (1999).

Example 4 – Statistical Methods

[00195] Samples from RA subjects and healthy subject were analyzed with the cell population and mass spectrometry platforms to look for significant differences between the two groups. Variables were compared with either an un-paired t-test or non-parametric test, as appropriate for each variable, using SAS™ software. The study includes multiple comparisons and caution is needed to consider potential false positive conclusions. The step-down Bonferroni p-value adjustment method of Holm was used maintain a study-wide p-value <0.05. Results are considered at both the adjusted and multiple-univariate statistical levels. Holm, S., A simple sequentially rejective multiple test procedure, in Scand J Stat. 1979. p. 65-70; Blair, et al., Control of familywise errors in multiple endpoint assessments via stepwise permutation tests. 1996. 15(11): p. 1107-1121.

Table 1. Identified Full Length Proteins Increased in Subjects having RA

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
109	NP_056472.2	27881501	ATP-binding cassette, sub-family A, member 12 isoform b; ATP-binding cassette A12 [Homo sapiens]	1	1	1.04	1.04	3.55×10^{-2}	5154
20	LPHUB	71789	apolipoprotein B-100 precursor - human	5	3	1.08	1.08	1.63×10^{-2}	6186
13	NP_000055.1	4557385	complement component 3 precursor [Homo sapiens]	7	6	1.11	1.11	2.28×10^{-2}	7592
30	NP_001176.1	4502337	alpha-2-glycoprotein 1, zinc; Alpha-2-glycoprotein, zinc [Homo sapiens]	4	2	1.12	1.12	2.21×10^{-2}	5327
32	NP_006211.1	5453896	serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 2; Protease inhibitor 1-like; protease inhibitor 1 (alpha-1-antitrypsin)-like [Homo sapiens]	3	2	1.13	1.13	9.91×10^{-4}	4696
80	NP_000574.1	9845255	group-specific component (vitamin D binding protein); hDBP [Homo sapiens]	1	1	1.16	1.16	1.12×10^{-2}	11431
95	NP_000286.2	21361198	serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1; Protease inhibitor (alpha-1-antitrypsin); protease inhibitor 1 (anti-elastase), alpha-1-antitrypsin [Homo sapiens]	2	1	1.17	1.17	2.99×10^{-2}	4055
46	P04004	139653	Vitronectin precursor (Serum spreading factor) (S-protein) (V75) [Contains: Vitronectin V65 subunit	1	1	1.20	1.20	3.54×10^{-2}	13378
35	NP_005742.4	22538387	A kinase anchor protein 9 isoform 2; yotiao; A-kinase anchoring protein 450; AKAP120-like protein [	2	2	1.20	1.20	1.11×10^{-2}	3677
87	NP_056039.1	14150229	retinoblastoma-associated protein RAP140 [Homo sapiens]	1	1	1.20	1.20	4.07×10^{-3}	5543
47	S23650	2120082	retrovirus-related hypothetical protein II - human retrotransposon LINE-1	1	1	1.24	1.24	4.82×10^{-2}	5372
77	NP_054790.1	7661976	nuclear receptor coactivator RAP250; peroxisome proliferator-act; nuclear receptor coactivator RAP2	1	1	1.26	1.26	1.88×10^{-2}	4810

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
33	JE0242	7438711	Ig kappa chain NIG26 precursor - human	3	2	1.27	1.27	1.25×10^{-2}	17201
23	P02774	139641	Vitamin D-binding protein precursor (DBP) (Group-specific component) (GC-globulin) (VDB)	3	3	1.29	1.29	2.45×10^{-2}	9854
49	C4HU	2144577	complement C4A precursor [validated] - human	1	1	1.29	1.29	3.62×10^{-2}	15496
84	NP_068774.1	11386179	guanine nucleotide binding protein (G protein), gamma transducing activity polypeptide 1 [Homo sapiens]	1	1	1.29	1.29	3.02×10^{-2}	2686
93	NP_624358.1	21264371	nucleoporin 98kD isoform 4; nucleoporin 98kD; Nup98-Nup96 precursor; GLFG-repeat containing nucleoporin [Homo sapiens]	2	1	1.29	1.29	2.73×10^{-3}	5421
19	NP_000629.2	18201911	vitronectin precursor; serum spreading factor; somatomedin B; complement S-protein [Homo sapiens]	7	4	1.30	1.30	1.35×10^{-2}	8182
2	P01009	1703025	Alpha-1-antitrypsin precursor (Alpha-1 protease inhibitor) (Alpha-1-antiproteinase) (PRO0684/PRO220	61	28	1.31	1.31	1.26×10^{-2}	10798
89	NP_064620.2	18378731	HMG-BOX transcription factor BBX; x 001 protein [Homo sapiens]	2	1	1.32	1.32	1.64×10^{-2}	2886
67	NP_004658.1	4758520	hect domain and RLD 2 [Homo sapiens]	1	1	1.33	1.33	1.42×10^{-2}	2964
107	NP_000710.3	27597080	calcium channel, voltage-dependent, L type, alpha 1C subunit [Homo sapiens]	1	1	1.34	1.34	1.78×10^{-2}	5196
28	P08697	112907	Alpha-2-antiplasmin precursor (Alpha-2-plasmin inhibitor) (Alpha-2-PI) (Alpha-2-AP)	4	2	1.34	1.34	7.75×10^{-3}	7171
50	Q99743	3914169	Neuronal PAS domain protein 2 (Neuronal PAS2) (Member of PAS protein 4) (MOP4)	1	1	1.34	1.34	2.28×10^{-2}	2228
45	P22932	133500	Retinoic acid receptor gamma-2 (RAR-gamma-2)	1	1	1.35	1.35	3.35×10^{-2}	5714
14	OMHU1B	69990	alpha-1-B-glycoprotein - human	7	5	1.36	1.36	1.55×10^{-2}	10348
29	P05546	123055	Heparin cofactor II precursor (HC-II) (Protease inhibitor leuserpin 2) (HLS2)	2	2	1.36	1.36	3.19×10^{-2}	4519
11	P01857	121039	Ig gamma-1 chain C region	13	8	1.37	1.37	2.57×10^{-2}	11550
69	NP_005521.1	5031777	isocitrate dehydrogenase 3 (NAD+) alpha precursor; H-IDH alpha; isocitric dehydrogenase; isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial; NAD+-specific	1	1	1.37	1.37	1.53×10^{-3}	3619

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
			ICDH; NAD(H)-specific isocitrate dehydrogenase alpha subunit precursor; isocitrate dehydrogenase (NAD+) alpha chain precursor [Homo sapiens]						
4	KUHU	1070458	ferroxidase (EC 1.16.3.1) precursor [validated] - human	33	22	1.38	1.38	1.30×10^{-2}	8872
106	XP_058831.3	27500444	similar to zona pellucida binding protein [Homo sapiens]	1	1	1.38	1.38	2.09×10^{-2}	2952
85	NP_061819.2	12056473	N-acetylneuraminic acid phosphate synthase; sialic acid synthase; sialic acid phosphate synthase [Homo sapiens]	1	1	1.38	1.38	3.33×10^{-3}	2985
73	NP_009049.1	6005922	triple functional domain (PTPRF interacting) [Homo sapiens]	1	1	1.39	1.39	3.76×10^{-3}	3615
76	NP_055433.1	7657009	deleted in bladder cancer chromosome region candidate 1 [Homo sapiens]	1	1	1.40	1.40	1.04×10^{-2}	2680
18	NP_000087.1	4557485	ceruloplasmin (ferroxidase); Ceruloplasmin [Homo sapiens]	4	4	1.40	1.40	2.41×10^{-2}	8960
96	NP_037533.2	21361440	RAB3A interacting protein (rabin3)-like 1 [Homo sapiens]	1	1	1.41	1.41	1.70×10^{-3}	2501
97	NP_055874.1	22035665	talin 2 [Homo sapiens]	2	1	1.41	1.41	1.32×10^{-2}	3952
37	XP_209546.1	27481320	similar to Ceruloplasmin precursor (Ferroxidase) [Homo sapiens]	3	2	1.42	1.42	8.20×10^{-3}	7687
10	NP_000598.1	9257232	orosomucoid 1 precursor; Orosomucoid-1 (alpha-1-acid glycoprotein-1); alpha-1-acid glycoprotein 1 [	20	10	1.43	1.43	8.37×10^{-3}	9788
27	S05270	87890	Ig lambda chain precursor - human	2	2	1.44	1.44	2.17×10^{-2}	4533
90	NP_004886.2	19923284	cold autoinflammatory syndrome 1; chromosome 1 open reading frame 7; angiotensin/vasopressin recept	2	1	1.44	1.44	3.41×10^{-3}	4848
104	XP_044347.3	27499033	similar to KIAA0913 protein [Homo sapiens]	1	1	1.44	1.44	1.05×10^{-2}	3764
65	NP_000326.1	4506809	sodium channel, voltage-gated, type V, alpha polypeptide [Homo sapiens]	1	1	1.45	1.45	2.65×10^{-2}	2741
78	NP_060549.1	8922392	hypothetical protein FLJ10379 [Homo sapiens]	1	1	1.45	1.45	4.68×10^{-2}	3053
31	NP_000599.1	4505529	orosomucoid 2; alpha-1-acid glycoprotein, type 2 [Homo sapiens]	4	2	1.46	1.46	2.14×10^{-2}	13328
21	P01876	113584	Ig alpha-1 chain C region	4	3	1.46	1.46	2.62×10^{-2}	15257

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
55	NP_001747.1	4502595	corticosteroid binding globulin precursor; corticosteroid binding globulin; alpha-1 anti-proteinase, antitrypsin [Homo sapiens]	1	1	1.47	1.47	5.70×10^{-3}	10918
44	P18136	125819	KV3M_HUMAN IG KAPPA CHAIN V-III REGION HIC PRECURSOR	1	1	1.47	1.47	2.26×10^{-2}	3923
22	P01871	127514	MUC_HUMAN Ig mu chain C region	3	3	1.50	1.50	2.68×10^{-2}	11044
102	XP_208769.1	27482513	similar to Ig gamma-2 chain C region [Homo sapiens]	1	1	1.51	1.51	4.40×10^{-2}	6233
51	NP_001076.1	4501843	alpha-1-antichymotrypsin, precursor; alpha-1-antichymotrypsin; antichymotrypsin [Homo sapiens]	2	1	1.53	1.53	2.09×10^{-2}	12502
68	NP_005112.1	4827044	thyroid hormone receptor-associated protein, 240 kDa subunit [Homo sapiens]	1	1	1.55	1.55	7.07×10^{-4}	2376
38	S15590	106378	Ig heavy chain - human	1	1	1.55	1.55	2.58×10^{-2}	12558
7	P01011	112874	Alpha-1-antichymotrypsin precursor (ACT)	17	11	1.57	1.57	7.69×10^{-3}	9697
98	XP_173158.1	22052041	hypothetical protein XP_173158 [Homo sapiens]	1	1	1.57	1.57	2.59×10^{-2}	2573
94	NP_112494.2	21314742	hypothetical protein DKFZp434G2226 [Homo sapiens]	1	1	1.60	1.60	4.65×10^{-3}	2618
3	NP_005134.1	4826762	haptoglobin [Homo sapiens]	57	28	1.60	1.60	1.42×10^{-2}	10657
43	P05155	124096	Plasma protease C1 inhibitor precursor (C1 Inh) (C1Inh)	1	1	1.61	1.61	3.69×10^{-3}	7962
42	P00737	123507	Haptoglobin-1 precursor	2	1	1.61	1.61	2.10×10^{-2}	24108
9	NP_443204.1	16418467	leucine-rich alpha-2-glycoprotein [Homo sapiens]	14	11	1.62	1.62	1.21×10^{-2}	9467
64	NP_000532.1	4506781	S-arrestin; S-antigen [Homo sapiens]	1	1	1.66	1.66	1.48×10^{-2}	3677
63	NP_000895.1	4505417	NAD(P)H dehydrogenase, quinone 2; NAD(P)H menadione oxidoreductase-1, di-oxin-inducible-2; NAD(P)H menadione oxi-doreductase 2, dioxin-inducible [Homo sapiens]	1	1	1.70	1.70	1.41×10^{-2}	3103
48	ANHU	2144576	angiotensin precursor [validated] - human	1	1	1.70	1.70	7.03×10^{-3}	2128
92	XP_057927.2	20535708	similar to KIAA1902 protein [Homo sapiens]	1	1	1.75	1.75	4.58×10^{-3}	5802
101	XP_043492.2	27477685	similar to KIAA1728 protein [Homo sapiens]	2	1	1.75	1.75	1.22×10^{-2}	2702
108	NP_775111.1	27765076	calpain 3 isoform d; calpain, large polypep-tide L3; calpain p94, large [catalytic] subunit;	1	1	1.77	1.77	1.74×10^{-2}	3103

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
			muscle-specific calcium-activated neutral protease 3 large subunit [Homo sapiens]						
100	NP_060606.2	24211029	asp (abnormal spindle)-like, microcephaly associated [Homo sapiens]	1	1	1.77	1.77	2.85×10^{-3}	2838
36	NP_066275.2	23821019	haptoglobin-related protein; Haptoglobin-related locus [Homo sapiens]	5	2	1.83	1.83	1.43×10^{-2}	13046
39	P01877	113585	Ig alpha-2 chain C region	1	1	1.88	1.88	1.39×10^{-2}	10360
83	T46372	11360168	hypothetical protein DKFZp434P1818.1 - human (fragment)	3	1	2.07	2.07	1.00×10^{-2}	6240
41	P01860	121045	GC3_HUMAN Ig gamma-3 chain C region (Heavy chain disease protein) (HDC)	1	1	2.34	2.34	6.35×10^{-4}	3746

Table 2. Identified Full Length Proteins Decreased in Subjects having RA

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
16	NP_000362.1	4507725	transthyretin (prealbumin, amyloidosis type I); Transthyretin (prealbumin) [Homo sapiens]	8	5	0.95	-1.05	1.65×10^{-2}	11714
24	NP_000497.1	4503635	coagulation factor II precursor; prothrombin [Homo sapiens]	3	3	0.93	-1.08	1.60×10^{-2}	10328
86	NP_001398.1	13325066	cadherin EGF LAG seven-pass G-type receptor 3; EGF-like-domain, multiple 1; epidermal growth factor	1	1	0.85	-1.17	4.67×10^{-2}	3976
1	NP_001054.1	4557871	transferrin [Homo sapiens]	73	47	0.85	-1.18	1.63×10^{-2}	12997
99	P57071	23503097	PRDF_HUMAN PR-domain zinc finger protein 15 (Zinc finger protein 298)	1	1	0.84	-1.19	1.73×10^{-2}	2646
59	NP_002206.1	4504781	inter-alpha (globulin) inhibitor, H1 polypeptide [Homo sapiens]	1	1	0.84	-1.19	2.50×10^{-2}	5952
103	XP_210868.1	27498981	hypothetical protein XP_210868 [Homo sapiens]	1	1	0.84	-1.20	2.03×10^{-2}	2548
75	T14760	7512615	hypothetical protein DKFZp434I213.1 - human (fragment)	1	1	0.83	-1.20	2.71×10^{-2}	2794
79	NP_060835.1	8922950	hypothetical protein FLJ11222 [Homo sapiens]	2	1	0.83	-1.20	2.17×10^{-2}	2758
34	NP_009117.2	21735548	centrosomal protein 2; centrosome associated protein; centrosomal Nek2-associated protein 1 [Homo s	3	2	0.83	-1.20	2.65×10^{-2}	5099
60	NP_000884.1	4504893	kininogen [Homo sapiens]	1	1	0.82	-1.21	1.65×10^{-2}	3783
6	NP_000468.1	4502027	albumin precursor; PRO0883 protein [Homo sapiens]	29	20	0.82	-1.22	1.67×10^{-2}	13267
105	XP_208509.1	27499046	hypothetical protein XP_208509 [Homo sapiens]	1	1	0.82	-1.22	3.36×10^{-2}	3549
81	NP_000604.1	11321561	hemopexin [Homo sapiens]	1	1	0.81	-1.23	3.35×10^{-2}	13690
5	NP_000005.1	4557225	alpha 2 macroglobulin precursor [Homo sapiens]	27	21	0.80	-1.26	1.92×10^{-2}	9829
56	NP_001422.1	4503579	erythrocyte membrane protein band 4.1-like 2 [Homo sapiens]	1	1	0.79	-1.26	1.93×10^{-2}	3089

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
72	NP_009185.1	6005836	polynucleotide kinase 3'-phosphatase; polynucleotide kinase 3-prime-phosphatase [Homo sapiens]	2	1	0.79	-1.26	2.72×10^{-2}	4218
17	NP_002207.1	4504783	inter-alpha (globulin) inhibitor, H2 polypeptide [Homo sapiens]	4	4	0.79	-1.26	3.22×10^{-2}	5550
74	JE0243	7438712	Ig kappa chain NIG93 precursor - human	1	1	0.79	-1.26	3.05×10^{-2}	3177
88	NP_056986.2	15147337	progestin induced protein; ubiquitin-protein ligase [Homo sapiens]	1	1	0.79	-1.27	1.82×10^{-2}	2705
61	NP_002334.1	4505043	lactotransferrin [Homo sapiens]	1	1	0.78	-1.28	1.28×10^{-2}	3510
52	NP_001613.1	4502005	alpha-2-HS-glycoprotein; Alpha-2HS-glycoprotein [Homo sapiens]	1	1	0.78	-1.28	3.60×10^{-3}	10104
70	NP_006613.1	5730055	serum-inducible kinase [Homo sapiens]	1	1	0.76	-1.31	1.32×10^{-3}	3578
15	NP_000479.1	4502261	serine (or cysteine) proteinase inhibitor, clade C (antithrombin), member 1; anti-thrombin III [Homo	6	5	0.76	-1.32	1.87×10^{-2}	9734
8	P19823	125000	Inter-alpha-trypsin inhibitor heavy chain H2 precursor (ITI heavy chain H2) (Inter-alpha-inhibitor 7	13	11	0.76	-1.32	1.43×10^{-2}	9269
53	NP_001624.1	4502067	alpha-1-microglobulin/bikunin precursor; Alpha-1-microglobulin/bikunin precursor; inter-alpha-trypsin; Alpha-1-microglobulin/bikunin precursor (inter-alpha-trypsin inhibitor, light chain; protein HC) [Homo sapiens]	1	1	0.75	-1.33	2.84×10^{-2}	2946
26	NP_000030.1	4557321	apolipoprotein A-I precursor [Homo sapiens]	4	3	0.75	-1.33	3.59×10^{-2}	13128
71	NP_006735.1	5803139	retinol-binding protein 4, plasma precursor; retinol-binding protein 4, plasma; retinol-binding protein 4, interstitial [Homo sapiens]	1	1	0.75	-1.34	6.13×10^{-4}	14481
82	T46477	11360087	hypothetical protein DKFZp434K1831.1 - human (fragment)	1	1	0.74	-1.35	3.29×10^{-2}	2830
54	NP_001634.1	4502149	apolipoprotein A-II precursor [Homo sapiens]	1	1	0.70	-1.44	2.86×10^{-2}	2228
91	NP_064547.2	20336302	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 33 [Homo sapiens]	1	1	0.69	-1.45	1.85×10^{-2}	2878
40	P01859	121043	Ig gamma-2 chain C region	2	1	0.67	-1.50	3.35×10^{-2}	13050
66	NP_000578.1	4557387	complement component 7 precursor [Homo sapiens]	1	1	0.65	-1.54	1.78×10^{-3}	6388

RA Marker #	Accession #	gi #	Protein Description	# Components	# Peptides	<Exp Ratio>	Fold Change	<P>	<Score>
62	NP_002336.1	4505047	lumican [Homo sapiens]	1	1	0.65	-1.55	1.77×10^{-6}	8166
25	NP_000549.1	4504347	alpha 1 globin [Homo sapiens]	4	3	0.62	-1.60	1.97×10^{-2}	8520
12	NP_000509.1	4504349	beta globin [Homo sapiens]	10	7	0.62	-1.61	1.54×10^{-2}	7791
58	NP_000510.1	4504351	delta globin [Homo sapiens]	1	1	0.59	-1.68	1.03×10^{-2}	19814
57	NP_000168.1	4504165	gelsolin (amyloidosis, Finnish type); Gel-solin [Homo sapiens]	1	1	0.14	-7.09	8.16×10^{-3}	4055

Table 3. Identified Protein Fragments Increased in Subjects having RA
(C* signifies carboxymethylation of C residue; M# signifies oxidation of M residue)

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
1	266	355.66	13.26	2	710.31	DSSLCK	1.58	P<0.05	185
1	1821	570.60	53.00	3	1709.78	LCMGSGLNLCEPNNK	1.45	P<0.01	184
1	3552	633.27	85.62	4	2530.06	SMGGKEDLIWELLNQAQEHFGK	1.42	P<0.05	183
1	1349	500.72	39.92	2	1000.43	YLGEEYVK	1.39	P<0.001	182
1	4360	550.99	55.39	4	2200.94	SDNC*EDTPEAGYFAVAVVKK	1.36	P<0.05	181
1	1274	489.49	61.98	4	1954.94	NLNEKDYELLCLDGTR	1.33	P<0.05	23
1	2860	854.91	48.87	2	1708.81	LCMGSGLNLCEPNNK	1.32	P<0.05	180
1	1818	570.27	48.92	3	1708.79	LCMGSGLNLCEPNNK	1.23	P<0.05	180
1	1494	520.72	24.11	2	1040.43	FSEGCAPGSK	1.21	P<0.05	179
1	1816	570.25	55.69	3	1708.73	LCMGSGLNLCEPNNK	1.16	P<0.05	180
1	768	427.96	48.84	4	1708.82	LCMGSGLNLCEPNNK	1.16	CountDiff	180
1	4725	1000.42	39.92	1	1000.42	YLGEEYVK	1.04	CountDiff	182
1	3844	794.86	35.79	2	1588.71	KPVEEYANCHLAR	1.02	CountDiff	8
2	3120	1321.19	74.14	3	3961.55	MFNIQHCKKLSSWVLLMKYLGNA-TAIFFLPDEGK	1.94	P<0.05	211
2	4107	1093.51	50.31	2	2186.01	LYHSEAFTVNFGDTEEAKK	1.62	P<0.001	210
2	2571	729.34	50.37	3	2186.00	LYHSEAFTVNFGDTEEAKK	1.60	P<0.001	210
2	1516	523.26	98.21	4	2090.02	ELDRDTVFALVNYIFFK	1.59	P<0.05	209
2	2448	697.35	98.24	3	2090.03	ELDRDTVFALVNYIFFK	1.57	P<0.05	209
2	2042	605.31	25.22	1	605.31	VPMMK	1.53	P<0.001	208
2	4617	729.32	52.07	3	2185.94	LYHSEAFTVNFGDTEEAKK	1.51	P<0.05	210
2	936	445.25	44.56	3	1333.73	LVDKFLEDVKK	1.47	P<0.05	207
2	3115	1288.15	71.37	2	2575.29	TLNQPDSQLQLTTGNGLFLSEGLK	1.46	P<0.05	206
2	2032	602.84	59.18	2	1204.67	KLSSWVLLMK	1.45	P<0.001	205
2	297	360.50	28.99	3	1079.48	FLENEDRR	1.44	P<0.001	204
2	157	336.86	27.66	3	1008.56	QINDYVEK	1.43	P<0.005	203
2	2967	946.42	47.25	2	1891.83	DTEEEDFHVDQVTTVK	1.43	P<0.05	202
2	298	360.50	27.54	3	1079.48	FLENEDRR	1.41	P<0.001	204
2	3074	1130.05	80.25	2	2259.09	GTEAAGAMFLEAIPMSIPPEVK	1.40	P<0.05	201
2	1558	529.73	14.49	2	1058.45	EDPQGDAAQK	1.40	P<0.001	200

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
2	871	438.00	50.28	5	2185.97	LYHSEAFTVNFGDTEEAKK	1.40	P<0.01	210
2	1385	505.23	33.46	2	1009.45	QINDYVEK	1.39	P<0.001	203
2	3022	1008.49	31.34	1	1008.49	QINDYVEK	1.39	P<0.005	203
2	4045	992.45	40.70	1	992.45	QINDYVEK	1.36	P<0.01	203
2	2899	888.49	35.91	1	888.49	AVLTIDEK	1.36	P<0.005	199
2	2183	631.27	47.32	3	1891.79	DTEEEDFHVDQVTTVK	1.35	P<0.005	202
2	1658	545.77	40.78	2	1090.53	WERPFEVK	1.35	P<0.005	198
2	2856	852.48	31.84	1	852.48	SASLHLPK	1.34	P<0.005	197
2	765	426.74	31.81	2	852.47	SASLHLPK	1.33	P<0.001	196
2	2710	779.40	37.54	1	779.40	SPLFMGK	1.31	P<0.005	195
2	1318	496.23	41.97	2	991.45	QINDYVEK	1.30	P<0.005	203
2	942	445.93	24.24	4	1780.70	TDTSHHDQDHPTFNK	1.30	P<0.005	194
2	572	402.22	59.19	3	1204.64	KLSSWVLLMK	1.29	P<0.001	205
2	1320	496.72	40.68	2	992.43	QINDYVEK	1.29	P<0.05	203
2	1621	540.25	28.98	2	1079.49	FLENEDRR	1.28	P<0.005	204
2	402	379.85	26.44	3	1137.53	KQINDYVEK	1.28	P<0.005	193
2	1617	539.75	26.15	2	1078.49	FLENEDRR	1.27	P<0.001	204
2	1383	505.24	30.47	2	1009.47	QINDYVEK	1.27	P<0.05	203
2	1806	568.79	28.87	2	1136.57	KQINDYVEK	1.27	P<0.005	193
2	2649	753.70	80.23	3	2259.08	GTEAAGAMFLEAIPMSIPPEVK	1.26	P<0.05	201
2	1321	496.73	43.77	2	992.45	QINDYVEK	1.26	P<0.01	203
2	3312	508.30	52.51	2	1015.59	SVLGQLGITK	1.26	P<0.001	192
2	1786	565.53	80.28	4	2259.10	GTEAAGAMFLEAIPMSIPPEVK	1.25	P<0.01	201
2	11	303.15	25.22	2	605.29	VPMMK	1.25	P<0.001	208
2	398	379.52	28.88	3	1136.54	KQINDYVEK	1.25	P<0.005	191
2	4557	301.92	59.04	4	1204.66	KLSSWVLLMK	1.24	CountDiff	205
2	255	353.48	14.49	3	1058.42	EDPQGDAAQK	1.23	P<0.05	200
2	1807	569.28	26.46	2	1137.55	KQINDYVEK	1.23	P<0.005	191
2	315	364.18	40.78	3	1090.52	WERPFEVK	1.23	P<0.05	198
2	3492	611.96	47.74	3	1833.86	VFSNGADLSGVTEEAPLK	1.21	P<0.05	190
2	3658	686.64	59.50	3	2057.90	LYHSEAFTVNFGDTEEAK	1.21	P<0.05	189
2	1670	547.94	80.71	3	1641.80	ITPNLAEFAFSLYR	1.21	P<0.01	188
2	2636	750.39	34.17	1	750.39	FLEDVK	1.21	P<0.05	187
2	4135	1204.70	59.07	1	1204.70	KLSSWVLLMK	1.20	CountDiff	205

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
2	1620	540.25	27.54	2	1079.49	FLENEDRR	1.19	P<0.05	204
2	3229	459.47	57.79	4	1834.86	VFSNGADLSGVTEEAPLK	1.17	P<0.01	190
2	1968	593.91	23.40	3	1779.71	TDTSHHDQDHPTFNK	1.17	P<0.05	194
2	272	356.94	24.24	5	1780.67	TDTSHHDQDHPTFNK	1.16	P<0.05	194
2	294	360.16	26.16	3	1078.46	FLENEDRR	1.16	P<0.005	204
2	2139	624.78	46.12	2	1248.55	LGMFNIQHCK	1.16	P<0.01	39
2	156	336.83	31.34	3	1008.47	QINDYVEK	1.15	P<0.05	203
2	1380	504.73	31.34	2	1008.45	QINDYVEK	1.10	P<0.01	186
2	675	416.84	46.11	3	1248.50	LGMFNIQHCK	1.09	P<0.005	39
2	491	390.19	37.54	2	779.37	SPLFMGK	1.09	P<0.05	195
2	929	444.72	35.91	2	888.43	AVLTIDEK	1.08	P<0.05	199
2	3461	594.25	24.23	3	1780.73	TDTSHHDQDHPTFNK	1.06	CountDiff	194
3	3420	570.29	33.93	3	1708.85	LRTEGDGVYTLNDKK	2.53	P<0.005	235
3	3071	1117.82	53.91	3	3351.44	VDSGNDVTDIADDGCPKPPEIAHGYVEHSVR	2.34	P<0.001	234
3	769	427.97	33.90	4	1708.86	LRTEGDGVYTLNDKK	2.28	P<0.005	235
3	2999	988.76	48.87	3	2964.26	LPECEADDGCPKPPEIAHGYVEHSVR	2.25	P<0.001	233
3	1967	593.65	48.19	5	2964.22	LPECEADDGCPKPPEIAHGYVEHSVR	2.18	P<0.05	233
3	1819	570.28	37.85	3	1708.82	LRTEGDGVYTLNDKK	2.15	P<0.001	235
3	2609	741.82	48.89	4	2964.26	LPECEADDGCPKPPEIAHGYVEHSVR	2.04	P<0.001	233
3	2544	720.84	33.43	2	1440.67	TEGDGVYTLNNEK	2.00	P<0.005	41
3	1965	593.66	48.80	5	2964.27	LPECEADDGCPKPPEIAHGYVEHSVR	1.99	P<0.005	233
3	2871	859.37	50.10	4	3434.46	AVGDKLPECEADDGCPKPPEIAHGYVEHSVR	1.89	P<0.001	178
3	2543	720.82	37.19	2	1440.63	TEGDGVYTLNNEK	1.87	P<0.001	41
3	2861	854.92	37.84	2	1708.83	LRTEGDGVYTLNDKK	1.82	P<0.005	235
3	1932	587.27	9.84	1	587.27	NYYK	1.81	P<0.05	232
3	2939	923.52	29.90	1	923.52	ILGGHLDAK	1.80	P<0.001	231
3	2498	709.90	54.12	2	1418.79	DIAPTLTLYVGKK	1.80	P<0.005	230
3	2995	980.48	41.32	1	980.48	VGYVSGWGR	1.76	P<0.001	229
3	2833	838.61	53.60	4	3351.42	VDSGNDVTDIADDGCPKPPEIAHGYVEHSVR	1.74	P<0.05	234
3	2945	930.43	41.11	2	1859.85	AVGDKLPECEAVCGKPK	1.72	P<0.001	228
3	1160	473.60	54.15	3	1418.78	DIAPTLTLYVGKK	1.70	P<0.005	230
3	3096	1203.63	48.75	1	1203.63	VTSIQDWVQK	1.67	P<0.005	227
3	2564	725.33	60.53	3	2173.97	SPVGVQPILNEHTFCAGMSK	1.67	P<0.001	226
3	2409	687.70	50.10	5	3434.47	AVGDKLPECEADDGCPKPPEIAHGYVEHSVR	1.65	P<0.001	178

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
3	1218	480.89	33.41	3	1440.65	TEGDGVYTLNNEK	1.62	P<0.01	41
3	973	449.54	49.09	3	1346.60	SCAVAEYGVYVK	1.60	P<0.05	225
3	2772	809.37	26.61	1	809.37	DYAEVGR	1.60	P<0.01	224
3	2595	739.35	25.15	1	739.35	NPANPVQ	1.59	P<0.005	223
3	2473	703.36	20.10	1	703.36	VSVNER	1.58	P<0.05	222
3	1212	480.55	35.92	3	1439.63	TEGDGVYTLNNEK	1.58	P<0.005	41
3	2841	841.45	47.55	1	841.45	QLVEIEK	1.56	P<0.005	221
3	2365	673.80	49.03	2	1346.59	SCAVAEYGVYVK	1.54	P<0.01	225
3	1069	462.26	29.89	2	923.51	ILGGHLDAK	1.51	P<0.001	231
3	709	421.22	47.56	2	841.43	QLVEIEK	1.49	P<0.005	221
3	1646	544.00	58.85	4	2172.98	SPVGVQPILNEHTFCAGMSK	1.49	P<0.005	226
3	2539	720.31	35.92	2	1439.61	TEGDGVYTLNNEK	1.48	P<0.005	41
3	2541	720.34	31.82	2	1439.67	TEGDGVYTLNDKK	1.47	P<0.005	220
3	2232	637.81	20.33	2	1274.61	HYEGSTVPEKK	1.42	P<0.05	219
3	2985	969.63	88.71	4	3875.50	YQEDTCYGDAGSAFAVHDLEEDTWYAT-GILSFDK	1.41	P<0.05	218
3	2355	671.09	53.87	5	3351.42	VDSGNDVTDIADDGCPKPPEIAHGYVEHSVR	1.41	P<0.01	234
3	3059	1087.01	58.86	2	2173.01	SPVGVQPILNEHTFCAGMSK	1.40	P<0.05	226
3	3116	1290.72	60.13	1	1290.72	DIAPTLTLYVGK	1.39	P<0.05	217
3	2312	656.29	36.35	2	1311.57	TEGDGVYTLNDK	1.38	P<0.05	216
3	1850	573.76	22.69	2	1146.51	HYEGSTVPEK	1.36	P<0.05	215
3	139	333.17	41.26	3	997.49	HTFCAGMSK	1.36	P<0.05	214
3	3123	1346.62	48.94	1	1346.62	SCAVAEYGVYVK	1.33	P<0.05	225
3	612	408.74	20.77	2	816.47	KQWINK	1.33	P<0.05	213
3	565	401.87	48.75	3	1203.59	VTSIQDWVQK	1.32	P<0.05	227
3	2123	620.62	41.12	3	1859.84	AVGDKLPECEAVCGKPK	1.31	P<0.001	228
3	802	430.90	60.12	3	1290.68	DIAPTLTLYVGK	1.29	P<0.05	217
3	110	327.49	41.31	3	980.45	VGYVSGWGR	1.27	P<0.05	229
3	247	352.18	20.09	2	703.35	VSVNER	1.26	P<0.05	212
3	2562	724.99	58.85	3	2172.95	SPVGVQPILNEHTFCAGMSK	1.23	P<0.05	226
3	1086	465.71	41.11	4	1859.82	AVGDKLPECEAVCGKPK	1.23	P<0.05	228
3	2266	645.85	60.13	2	1290.69	DIAPTLTLYVGK	1.22	P<0.05	217
3	29	308.50	29.88	3	923.48	ILGGHLDAK	1.19	P<0.05	231
3	1284	490.72	41.32	2	980.43	VGYVSGWGR	1.17	P<0.01	229
3	4748	1311.60	36.30	1	1311.60	TEGDGVYTLNDK	1.16	CountDiff	216

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
3	2028	602.29	48.75	2	1203.57	VTSIQDWVQK	1.15	P<0.05	227
4	1140	471.74	26.99	2	942.47	YTVNQCR	1.94	P<0.05	258
4	1561	529.91	39.96	3	1587.71	RQSEDSTFYLGER	1.57	P<0.001	257
4	2643	752.71	48.24	3	2256.11	KAEEEHLGILGPQLHADVGDK	1.52	P<0.01	266
4	67	316.67	22.82	2	632.33	VFNPR	1.48	P<0.005	255
4	2401	686.37	58.92	2	1371.73	GAYPLSIEPIGVR	1.47	P<0.005	254
4	2729	788.91	79.06	2	1576.81	DLYSGLIGPLIVCR	1.45	P<0.01	253
4	2584	735.96	56.77	3	2205.86	MHSMNGFMYGNQPGLTMCK	1.45	P<0.05	252
4	1864	575.78	49.78	4	2300.10	KLISVDTEHSNIYLQNGPDR	1.43	P<0.005	251
4	2748	794.36	39.93	2	1587.71	RQSEDSTFYLGER	1.41	P<0.05	257
4	2026	602.26	35.20	2	1203.51	EYTDASFTNR	1.41	P<0.01	250
4	2809	829.75	82.88	3	2487.23	GPEEEHLGILGPVIWAEVGDTIR	1.39	P<0.05	249
4	2013	600.27	68.78	4	2398.06	HYYIGIIETTWDYASDHGEK	1.39	CountDiff	248
4	3802	767.38	49.80	3	2300.12	KLISVDTEHSNIYLQNGPDR	1.38	P<0.01	251
4	1780	564.78	48.24	4	2256.10	KAEEEHLGILGPQLHADVGDK	1.37	P<0.05	266
4	1934	587.77	39.28	2	1174.53	MYYSAVDPTK	1.36	P<0.01	247
4	1401	509.22	31.00	2	1017.43	QYTDSTFR	1.36	P<0.005	246
4	1536	526.27	79.07	3	1576.79	DLYSGLIGPLIVCR	1.35	P<0.05	253
4	2666	760.36	57.82	2	1519.71	ALYLQYTDETFR	1.35	P<0.05	245
4	2705	775.36	63.08	5	3872.77	NMATRPYSI-HAHGVQTESSTVTPTLPGETLTYVWK	1.35	P<0.05	224
4	2558	724.35	51.55	3	2171.03	LISVDTEHSNIYLQNGPDR	1.35	P<0.05	243
4	2583	735.90	75.75	2	1470.79	DIASGLIGPLIICK	1.34	P<0.05	242
4	1286	490.93	75.75	3	1470.77	DIASGLIGPLIICK	1.34	P<0.05	242
4	2586	736.34	45.93	2	1471.67	EVGPTNADPVCLAK	1.33	P<0.005	241
4	1397	507.70	24.45	2	1014.39	TYCSEPEK	1.33	P<0.05	240
4	512	394.20	26.12	3	1180.58	IYHSHIDAPK	1.32	P<0.01	239
4	1135	471.20	25.73	2	941.39	YTVNQCR	1.30	P<0.005	258
4	1573	532.56	26.31	3	1595.66	VDKDNEDFQESNR	1.30	P<0.05	238
4	1574	532.76	51.91	4	2128.02	AEEEHLGILGPQLHADVGDK	1.28	P<0.05	237
4	2499	710.02	51.91	3	2128.04	AEEEHLGILGPQLHADVGDK	1.26	P<0.05	237
4	1862	575.55	48.94	4	2299.18	KLISVDTEHSNIYLQNGPDR	1.14	CountDiff	251
4	3929	854.90	82.74	4	3416.58	QKDVDKEFYLFPTVFDENESLLLEDNIR	1.10	CountDiff	236
5	2667	760.39	23.11	1	760.39	VDSHFR	1.60	P<0.001	259
5	409	380.69	23.09	2	760.37	VDSHFR	1.35	P<0.05	259

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
6	1774	564.27	58.75	3	1690.79	VFDEFKPLVEEPQN	1.48	P<0.05	263
6	3016	1000.59	48.12	1	1000.59	QTALVELVK	1.46	P<0.05	262
6	293	359.82	26.81	3	1077.44	NECFLQHK	1.30	CountDiff	261
6	4758	567.28	85.77	3	1699.82	RHPYFYAPELLFF	1.11	CountDiff	260
7	2684	766.36	34.14	1	766.36	DSLEFR	2.03	P<0.001	275
7	3139	331.85	34.23	3	993.53	KLINDYVK	1.74	CountDiff	274
7	436	383.68	34.14	2	766.35	DSLEFR	1.74	P<0.001	275
7	3797	766.05	95.21	3	2296.13	DYNLNDILLQLGIEEAFTSK	1.72	P<0.005	273
7	2184	631.28	57.32	3	1891.82	LYGSEAFATDFQDSAAAK	1.66	P<0.005	272
7	2898	887.11	86.85	3	2659.31	FNRPFLMIIVPTDTQNIFFMSK	1.65	P<0.05	271
7	129	331.52	34.08	3	992.54	KLINDYVK	1.60	P<0.01	274
7	3623	665.58	86.85	4	2659.30	FNRPFLMIIVPTDTQNIFFMSK	1.58	P<0.05	271
7	2968	946.43	57.21	2	1891.85	LYGSEAFATDFQDSAAAK	1.55	CountDiff	272
7	2508	711.82	54.99	2	1422.63	DEELSCTVVELK	1.55	P<0.005	270
7	1322	496.78	34.08	2	992.55	KLINDYVK	1.53	P<0.005	274
7	594	405.90	69.11	3	1215.68	ITLLSALVETR	1.52	P<0.05	269
7	3544	631.62	59.32	3	1892.84	LYGSEAFATDFQDSAAAK	1.48	P<0.01	272
7	1214	480.75	37.54	2	960.49	ADLSGITGAR	1.47	P<0.01	264
7	323	365.54	34.44	3	1094.60	NLAVSQVVHK	1.46	P<0.01	267
7	1984	596.97	63.89	3	1788.89	MEEVEAMLLPETLKR	1.45	P<0.01	266
7	2061	608.35	69.09	2	1215.69	ITLLSALVETR	1.43	P<0.01	269
7	1668	547.81	34.44	2	1094.61	NLAVSQVVHK	1.40	P<0.05	267
7	2979	954.47	63.24	2	1907.93	AVLDVFEEGTEASAATAVK	1.36	P<0.05	265
7	4027	960.50	37.56	1	960.50	ADLSGITGAR	1.35	CountDiff	264
8	1438	514.27	39.16	2	1027.53	TEVNVLPGAK	1.31	CountDiff	86
9	2191	631.99	78.41	3	1893.95	ENQLEVLEVSWLHGLK	1.92	P<0.001	286
9	671	416.69	23.35	2	832.37	CAGPEAVK	1.78	P<0.001	285
9	445	384.86	38.38	3	1152.56	ALGHLDLSGNR	1.75	P<0.001	284
9	1950	590.33	58.67	2	1179.65	DLLLPQPDLR	1.72	P<0.001	283
9	2383	679.68	72.68	3	2037.02	TLDLGENQLETLPPDLLR	1.70	P<0.001	282
9	2607	740.88	74.39	4	2960.50	LQELHLSSNGLESLSPEFLRPVPQLR	1.70	P<0.005	281
9	2808	829.35	78.18	3	2486.03	DGFDISGNPWICDQNLSDLYR	1.67	P<0.01	280
9	600	406.72	34.62	2	812.43	GPLQLER	1.62	P<0.001	279
9	985	450.77	38.00	2	900.53	GQTLLAVAK	1.58	P<0.05	278

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
9	646	413.17	32.12	2	825.33	DCQVFR	1.55	P<0.001	277
9	4677	740.64	73.67	4	2959.54	LQELHLSSNGLESLSPEFLRPVPQLR	1.51	CountDiff	281
9	4592	576.79	38.33	2	1152.57	ALGHLDLSGNR	1.49	P<0.05	284
9	2712	780.76	89.68	3	2340.26	NALTGLPPGLFQASATLDTLVLK	1.46	P<0.05	276
9	4728	1019.02	72.69	2	2037.03	TLDLGENQLETLPPDLLR	1.37	P<0.05	282
9	4771	947.48	78.41	2	1893.95	ENQLEVLEVSWLHGLK	1.35	CountDiff	286
9	2915	900.44	37.14	1	900.44	GQTLLAVAK	1.32	P<0.05	278
9	511	393.89	58.68	3	1179.65	DLLLPQPDLR	1.24	CountDiff	283
9	3220	450.75	39.00	2	900.49	GQTLLAVAK	1.16	CountDiff	278
9	4778	1243.52	78.23	2	2486.03	DGFDISGNPWICDQNLSDLYR	1.11	CountDiff	280
10	2870	859.12	79.89	4	3433.46	NWGLSVYADKPETTKEQLGEFYEALDC*LR	2.16	P<0.05	295
10	654	414.20	37.69	3	1240.58	SDVVYTDWKK	1.89	P<0.01	294
10	4066	1019.45	23.19	1	1019.45	DKCEPLEK	1.63	CountDiff	293
10	3514	620.80	37.67	2	1240.59	SDVVYTDWKK	1.63	P<0.005	294
10	2554	723.32	59.69	2	1445.63	TYMLAFDVNDEK	1.55	P<0.05	292
10	2720	784.61	69.90	4	3135.42	TYMLAFDVNDEKNWGLSVYADKPETTK	1.51	P<0.001	291
10	1229	482.55	57.42	3	1445.63	TYMLAFDVNDEK	1.49	P<0.001	292
10	429	383.18	15.73	3	1147.52	KDKCEPLEK	1.48	P<0.005	290
10	2553	723.31	57.42	2	1445.61	TYMLAFDVNDEK	1.46	P<0.001	292
10	2706	776.34	23.12	1	776.34	CEPLEK	1.45	P<0.005	289
10	465	387.52	67.40	3	1160.54	WFYIASAFR	1.43	P<0.001	97
10	3086	1160.57	67.41	1	1160.57	WFYIASAFR	1.40	P<0.01	97
10	1408	510.23	23.19	2	1019.45	DKCEPLEK	1.39	P<0.001	293
10	3428	574.28	15.72	2	1147.55	KDKCEPLEK	1.34	P<0.05	288
10	2882	872.36	73.90	2	1743.71	EQLGEFYEALDCLR	1.33	P<0.005	287
10	1901	581.92	73.90	3	1743.74	EQLGEFYEALDCLR	1.32	P<0.001	287
10	3067	1112.51	43.25	1	1112.51	SDVVYTDWK	1.29	P<0.05	294
10	180	340.48	23.19	3	1019.42	DKCEPLEK	1.29	P<0.01	293
10	479	388.66	23.11	2	776.31	CEPLEK	1.21	P<0.05	289
10	1895	580.77	67.40	2	1160.53	WFYIASAFR	1.17	P<0.005	97
10	4079	1045.81	69.87	3	3135.41	TYMLAFDVNDEKNWGLSVYADKPETTK	1.16	CountDiff	291
11	1744	560.26	55.53	3	1678.76	FNWYVDGVEVHNAK	1.79	P<0.05	300
11	4157	1322.65	48.52	1	1322.65	STSGGTAALGCLVK	1.68	P<0.01	299
11	2835	839.38	54.16	2	1677.75	FNWYVDGVEVHNAK	1.68	P<0.005	300

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
11	1593	535.74	59.48	4	2139.94	TPEVTCVVVDVSHEDPEVK	1.62	P<0.05	198
11	1740	559.92	54.07	3	1677.74	FNWYVDGVEVHNAK	1.61	P<0.005	300
11	2340	668.30	71.35	5	3337.47	SCDKTHTCPPCPAPELLGGPSVFLFPPKPK	1.56	P<0.05	297
11	1743	560.26	56.82	3	1678.76	FNWYVDGVEVHNAK	1.54	P<0.05	300
11	899	441.55	48.52	3	1322.63	STSGGTAALGCLVK	1.49	P<0.05	299
11	2523	713.99	59.48	3	2139.95	TPEVTCVVVDVSHEDPEVK	1.35	P<0.05	198
11	2820	835.42	35.66	1	835.42	DTLMISR	1.33	P<0.05	296
11	2328	661.81	48.52	2	1322.61	STSGGTAALGCLVK	1.33	P<0.05	299
12	1860	575.33	36.62	2	1149.65	VVAGVANALAHK	1.00	CountDiff	99
13	4206	385.22	29.34	2	769.43	VVPEGIR	1.44	P<0.01	302
13	2049	606.29	64.08	3	1816.85	SNLDEDIIAEENIVSR	1.17	P<0.05	301
14	1601	538.00	61.93	4	2148.98	IFFHLNAVALGDGGHYTCR	1.46	P<0.01	306
14	808	431.73	47.11	4	1723.90	LELHVDGPPPRPQLR	1.41	P<0.01	305
14	4039	987.48	39.95	1	987.48	CLAPLEGAR	1.38	P<0.05	304
14	2529	717.00	61.93	3	2148.98	IFFHLNAVALGDGGHYTCR	1.37	P<0.01	306
14	1309	494.24	39.92	2	987.47	CLAPLEGAR	1.22	P<0.05	304
14	12	303.18	35.81	2	605.35	FALVR	1.18	P<0.05	303
16	250	352.67	21.82	2	704.33	VEIDTK	1.61	P<0.05	307
16	1018	456.25	59.04	3	1366.73	GSPAINVAVHVFR	1.39	P<0.005	115
18	1680	549.94	53.10	3	1647.80	KALYLQYTDETFR	1.53	P<0.05	311
18	2276	648.51	38.14	4	2591.02	TYC*SEPEKVDKDNEDFQESNR	1.49	P<0.005	310
18	4103	1089.12	72.07	3	3265.34	VYPGEQYTYMLLATEEQSPGEGDGNC*VTR	1.35	P<0.05	309
18	2086	613.26	37.16	2	1225.51	DDEEFIESNK	1.25	P<0.05	308
19	1375	504.28	41.91	2	1007.55	IYISGMAPR	1.53	P<0.05	313
19	1709	556.27	52.56	3	1666.79	DWHGVPGQVDAAMAGR	1.48	P<0.01	312
19	2304	653.79	36.97	2	1306.57	GQYC*YELDEK	1.37	P<0.005	124
19	2301	653.26	40.78	2	1305.51	GQYC*YELDEK	1.36	P<0.05	124
19	852	436.19	36.96	3	1306.55	GQYC*YELDEK	1.32	P<0.01	124
19	109	327.39	36.97	4	1306.54	GQYC*YELDEK	1.32	P<0.01	124
19	4520	833.88	52.52	2	1666.75	DWHGVPGQVDAAMAGR	1.20	CountDiff	312
20	451	386.19	44.02	3	1156.55	SPAFTDLHLR	1.37	P<0.005	315
20	453	386.23	50.27	3	1156.67	SPAFTDLHLR	1.31	P<0.05	315
20	317	364.23	34.28	2	727.45	LAIPEGK	1.28	P<0.005	314
21	2928	918.44	56.38	2	1835.87	QEPSQGTTTFAVTSILR	1.60	P<0.005	319

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
21	4136	1213.62	44.11	1	1213.62	WLQGSQELPR	1.45	P<0.05	318
21	2083	612.62	56.39	3	1835.84	QEPSQGTTTFAVTSILR	1.40	P<0.005	317
21	2785	818.39	28.77	1	818.39	VAAEDWK	1.38	P<0.05	316
22	3272	489.25	45.65	3	1465.73	SKLIC*QATGFSPR	1.68	P<0.05	322
22	3678	695.08	54.13	4	2777.30	YAATSQVLLPSKDVMQGTDEHVVC*K	1.50	P<0.05	321
22	684	417.84	44.18	3	1251.50	LIC*QATGFSPR	1.33	P<0.05	320
23	4130	1183.62	101.59	2	2366.23	VPTADLEDVLPLAEDITNILSK	1.34	P<0.05	325
23	2756	799.48	34.81	1	799.48	VLEPTLK	1.27	P<0.05	324
23	2456	699.25	52.46	3	2095.73	SLGECCDVEDSTTCFNAK	1.25	P<0.05	323
24	4723	998.50	66.65	2	1995.99	LAVTTHGLPCLAWASAQAK	1.12	CountDiff	326
24	2593	738.65	55.62	3	2213.93	DKLAAC*LEGNC*AEGLGTNYR	1.10	CountDiff	127
26	4781	516.26	31.65	2	1031.51	LSPLGEEMR	1.26	CountDiff	328
27	1892	580.03	74.20	4	2317.10	QSNNKYAASSYLSLTPEQWK	1.54	P<0.05	133
27	773	428.26	35.58	2	855.51	LTVLGQPK	1.33	P<0.05	329
27	4589	553.77	92.73	4	2212.06	ATLVCLISDFYPGAVTVAWK	1.16	CountDiff	328
27	3064	1106.55	92.76	2	2212.09	ATLVCLISDFYPGAVTVAWK	1.06	CountDiff	328
28	641	412.22	48.67	3	1234.64	LCQDLGPGAFR	1.40	P<0.01	330
29	232	349.72	34.08	2	698.43	EVLLPK	1.42	P<0.05	332
29	1087	465.74	55.72	2	930.47	FAFNLYR	1.30	P<0.05	331
30	3800	766.89	40.94	2	1532.77	QKWEAEPVYVQR	1.37	P<0.05	333
30	1752	561.24	39.93	2	1121.47	QVEGMEDWK	1.23	P<0.05	135
31	3080	1144.48	45.56	1	1144.48	SDVMYTDWK	1.77	P<0.005	334
31	1834	572.74	45.58	2	1144.47	SDVMYTDWK	1.46	P<0.005	334
31	3046	1057.95	81.30	2	2114.89	EQLGEFYEALDCLCIPR	1.35	P<0.05	136
31	2480	705.63	81.30	3	2114.87	EQLGEFYEALDCLCIPR	1.26	P<0.05	136
32	401	379.85	30.87	3	1137.53	EQINNYVEK	1.44	P<0.001	335
32	3418	569.28	30.85	2	1137.55	EQINNYVEK	1.34	P<0.005	335
33	4089	1068.47	40.91	2	2135.93	VDNALQSGNSQESVTEQDSK	1.72	P<0.001	337
33	2511	712.65	40.90	3	2135.93	VDNALQSGNSQESVTEQDSK	1.54	P<0.001	336
34	2675	762.36	62.95	1	762.36	TQQRNN	1.35	P<0.05	338
35	370	373.69	31.00	2	746.37	LELSQR	1.76	P<0.05	339
36	4306	493.78	30.24	2	986.55	KQLVEIEK	1.99	P<0.05	341
36	4514	790.89	38.17	2	1580.77	LRTEGDGVYTLNDK	1.98	P<0.01	340
36	1548	527.59	38.18	3	1580.75	LRTEGDGVYTLNDK	1.96	P<0.01	340

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
36	4336	527.92	39.48	3	1581.74	LRTEGDGVYTLNDK	1.63	P<0.05	340
36	120	329.52	30.18	3	986.54	KQLVEIEK	1.59	P<0.005	341
37	2976	952.40	39.38	2	1903.79	NNEGTYYSPNYNPQSR	1.45	P<0.01	343
37	2844	844.40	60.33	3	2531.18	SVPPSASHVAPTETFTYEWTVPK	1.41	P<0.01	342
37	2216	635.27	39.39	3	1903.79	NNEGTYYSPNYNPQSR	1.40	P<0.05	343
37	2201	633.55	60.33	4	2531.18	SVPPSASHVAPTETFTYEWTVPK	1.02	CountDiff	342
38	1661	546.64	84.80	3	1637.90	VFAIPPSFASIFLTK	1.55	P<0.05	344
39	3438	583.25	51.94	5	2912.22	HYTNPSQDVTVPCPVPPPPPCCHPR	1.88	P<0.05	345
41	1718	557.79	70.85	4	2228.14	VVSVLTVLHQNWLDGKEYK	2.34	P<0.001	346
42	2353	670.89	52.88	5	3350.42	VDSGNDVTDIADDGCPKPPEIAHGYVEHSVR	1.97	P<0.01	234
42	2354	670.89	53.18	5	3350.42	VDSGNDVTDIADDGCPKPPEIAHGYVEHSVR	1.26	P<0.05	234
43	2072	610.32	46.96	2	1219.63	DFTCVHQALK	1.61	P<0.005	347
44	1279	490.27	40.13	2	979.53	LLIYGASSR	1.47	P<0.05	348
45	711	421.57	50.27	3	1262.69	KAACLDILMLR	1.35	P<0.05	349
46	1677	549.60	77.21	3	1646.78	DVWGIEGPIDAAFTR	1.20	P<0.05	350
47	26	307.17	29.58	3	919.49	EDTNKWK	1.24	P<0.05	351
48	4695	463.73	23.52	2	926.45	AVYDQSATA	1.70	P<0.01	353
48	3596	655.36	43.34	3	1964.06	ANAGKPKDPTFIPAPIQAK	1.09	CountDiff	352
49	4479	684.35	77.89	2	1367.69	DSSTWLTAFVLK	1.18	CountDiff	354
50	1598	537.30	61.22	2	1073.59	PMPVLLMGQA	1.34	P<0.05	355
51	2394	683.33	52.43	3	2047.97	RLYGSEAFATDFQDSAAAK	2.19	P<0.01	146
55	800	430.81	56.63	5	2150.02	SETEIHQGFQHLHQLFAK	1.47	P<0.01	356
55	1603	538.25	64.49	4	2149.98	SETEIHQGFQHLHQLFAK	1.06	CountDiff	356
60	4760	579.78	62.41	2	1158.55	KYFIDFVAR	1.30	CountDiff	357
63	1822	570.61	39.19	3	1709.81	EEPIPC*TAHWHFGQ	1.70	P<0.05	358
64	1094	466.55	51.68	3	1397.63	HNLKDAGEAEEGK	1.66	P<0.05	359
65	332	366.42	33.97	4	1462.66	GLSRTSMKPRSSR	1.45	P<0.05	360
67	510	393.68	59.71	2	786.35	DSSYMPS	1.33	P<0.05	361
68	1912	583.37	41.93	1	583.37	LPLIK	1.55	P<0.001	362
69	2063	608.81	65.25	2	1216.61	IAEFAFEYAR	1.37	P<0.005	363
69	597	406.20	65.25	3	1216.58	IAEFAFEYAR	1.12	CountDiff	363
73	540	398.86	31.96	3	1194.56	EGKLENGYRK	1.39	P<0.005	364
76	2071	610.32	43.07	3	1828.94	PQLDLFSCMLKHRLK	1.40	P<0.05	365
77	2536	719.68	70.47	3	2157.02	EAPTSLSQLLDNSGAPNVTIK	1.26	P<0.05	366

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
78	4587	537.76	39.08	2	1074.51	KVNEKDVDK	1.45	P<0.05	367
79	1347	500.27	40.19	2	999.53	AAYMNKER	1.09	CountDiff	163
80	4074	1028.93	54.73	2	2056.85	GQELC*ADYSENTFTEYK	1.16	P<0.05	368
83	113	327.84	35.07	3	981.50	KNGNVANYV	2.61	P<0.01	369
83	112	327.84	34.08	3	981.50	KNGNVANYV	2.35	P<0.005	369
83	1283	490.71	32.04	2	980.41	KNGNVANYV	1.26	P<0.05	369
84	2497	709.81	59.62	2	1418.61	M#PVINIEDLTEK	1.29	P<0.05	370
85	198	343.53	54.20	3	1028.57	LGKSVVAKVK	1.38	P<0.005	371
87	885	439.74	29.59	2	878.47	IM#KDVQK	1.20	P<0.005	372
88	1412	510.30	54.39	2	1019.59	EEAIAVTMR	1.09	CountDiff	167
89	2127	621.31	55.34	3	1861.91	ANPGYKWC*PTTNKPVK	1.38	P<0.05	373
89	1089	466.23	53.39	4	1861.90	ANPGYKWC*PTTNKPVK	1.26	P<0.05	373
90	712	421.56	65.13	3	1262.66	LGDFGIRLLCVG	1.46	P<0.005	374
90	3545	631.86	65.15	2	1262.71	LGDFGIRLLCVG	1.42	P<0.005	374
92	1009	453.48	61.83	4	1810.90	FDDQNLRSVNGAEITM	1.75	P<0.005	375
92	1008	453.48	63.16	4	1810.90	FDDQNLRSVNGAEITM	1.63	CountDiff	375
93	5	300.89	36.97	4	1200.54	ELDSQLNEPR	1.31	P<0.005	376
93	557	400.85	36.97	3	1200.53	ELDSQLNEPR	1.28	P<0.005	376
94	3038	1045.53	49.91	1	1045.53	KTTNQNVIK	1.60	P<0.005	377
95	290	359.53	64.79	3	1076.57	LSSWVLLMK	1.17	P<0.05	378
95	1612	538.79	64.80	2	1076.57	LSSWVLLMK	1.16	P<0.05	378
96	175	339.91	33.97	4	1356.62	TLVITSTPASPNR	1.41	P<0.005	379
97	395	378.87	54.20	3	1134.59	KGAAKVMVTNV	1.42	P<0.01	380
97	1800	567.80	54.20	2	1134.59	KGAAKVMVTNV	1.41	P<0.05	380
98	2118	619.64	70.80	3	1856.90	TEM#RNSENKNIFCVR	1.57	P<0.05	381
100	2314	656.79	37.28	2	1312.57	TQTVECTQTGSV	1.77	P<0.005	382
101	2642	752.32	51.69	2	1503.63	KMKEAAQRYQYA	1.81	P<0.005	383
101	1358	501.88	51.70	3	1503.62	KMKEAAQRYQYA	1.69	P<0.05	383
101	1359	502.22	53.13	3	1504.64	KMKEAAQRYQYA	1.15	CountDiff	383
102	1134	470.92	48.06	3	1410.74	PREEQFNSTFR	1.51	P<0.05	384
104	2573	730.34	55.04	3	2189.00	MGPGGGKAKALGGAGSGSKGSAGGGSK	1.44	P<0.05	385
106	2557	724.33	60.23	3	2170.97	TGNNRINITETGQLMVKDF	1.38	P<0.05	386
107	3188	419.20	43.79	2	837.39	LELFMGK	1.34	P<0.05	387
108	1840	573.00	57.32	4	2288.98	ELGVDQESEEGKGKTSPDKQK	1.77	P<0.05	388

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
109	834	433.70	35.46	2	866.39	NANAVCDT	1.04	P<0.05	389
115	1392	506.78	66.28	2	1012.55	MPQVFNFL	1.62	CountDiff	390
116	2865	857.43	61.84	2	1713.85	IAPQLSTEELVSLGEK	1.26	CountDiff	391
117	2206	634.01	74.34	3	1900.01	ECGKAFYSGSSLTQHQR	1.10	CountDiff	392
118	2158	626.85	57.53	2	1252.69	FVPQDVPPEPK	1.07	CountDiff	393
119	4195	359.67	43.13	2	718.33	LTLDEK	1.32	CountDiff	394
120	4701	622.28	46.24	3	1864.82	DIQMTQSPSSVSASVGDR	5.18	CountDiff	395

Table 4. Identified Protein Fragments Decreased in Subjects having RA

RA Marker #	Fragment #	m/z	R.T. (min.)	z	M+H	Peptide	Fold Change	P used	SEQ ID NO:
1	2489	708.82	47.06	2	1416.63	SVIPSDGPSVACVK	-1.11	P<0.05	38
1	774	428.52	47.75	3	1283.54	EGYYGYTGAFR	-1.12	P<0.05	37
1	2324	659.78	32.05	2	1318.55	WCAVSEHEATK	-1.12	P<0.05	36
1	1275	489.72	38.31	2	978.43	DGAGDVAFVK	-1.12	P<0.005	35
1	1645	543.93	62.19	3	1629.77	EDPQTFYYAVAVVK	-1.13	P<0.01	34
1	2251	642.26	47.74	2	1283.51	EGYYGYTGAFR	-1.13	P<0.01	37
1	414	381.42	44.02	4	1522.66	LKCDEWSVNSVGK	-1.15	P<0.05	33
1	1398	508.22	44.02	3	1522.64	LKCDEWSVNSVGK	-1.16	P<0.001	33
1	58	315.18	16.87	2	629.35	AVGNLR	-1.16	P<0.05	32
1	1306	493.57	62.53	3	1478.69	MYLGYEYVTAIR	-1.16	P<0.05	31
1	2671	761.85	44.03	2	1522.69	LKCDEWSVNSVGK	-1.17	P<0.05	33
1	1995	598.75	27.73	2	1196.49	WCALSHHER	-1.17	P<0.01	30
1	928	444.69	10.13	2	888.37	SCHTAVGR	-1.18	P<0.05	29
1	2732	789.38	72.33	2	1577.75	TAGWNIPMGLLYNK	-1.18	P<0.05	28
1	1992	598.26	44.19	2	1195.51	DSGFQMNQLR	-1.18	P<0.005	27
1	541	399.18	44.19	3	1195.52	DSGFQMNQLR	-1.18	P<0.05	27
1	2598	739.85	62.52	2	1478.69	MYLGYEYVTAIR	-1.18	P<0.05	31
1	3928	853.85	54.27	2	1706.69	FDEFFSEGC*APGSKK	-1.18	CountDiff	26
1	1063	461.68	31.61	2	922.35	DDTVCLAK	-1.19	P<0.001	25
1	1478	518.97	60.75	4	2072.86	SDNCEDTPEAGYFAVAVVK	-1.20	P<0.05	24
1	1539	526.59	72.31	3	1577.75	TAGWNIPMGLLYNK	-1.20	P<0.05	28
1	2425	691.62	60.77	3	2072.84	SDNCEDTPEAGYFAVAVVK	-1.20	P<0.005	24
1	1811	569.57	51.09	3	1706.69	FDEFFSEGC*APGSKK	-1.21	P<0.05	26
1	2292	651.96	58.15	3	1953.86	NLNEKDYELLCLDGTR	-1.21	P<0.05	23
1	2674	762.34	46.07	2	1523.67	LKCDEWSVNSVGK	-1.21	P<0.05	33
1	1423	511.88	58.92	3	1533.62	CSTSSLLEACTFR	-1.22	P<0.005	22
1	653	414.19	30.59	2	827.37	NPDPWAK	-1.22	P<0.005	21
1	729	423.45	39.76	4	1690.78	DCHLAQVPSHTVVAR	-1.22	P<0.05	20
1	2686	767.30	58.92	2	1533.59	CSTSSLLEACTFR	-1.22	P<0.005	22
1	1773	564.27	39.76	3	1690.79	DCHLAQVPSHTVVAR	-1.24	P<0.01	20

1	2936	922.40	31.62	1	922.40	DDTVCLAK	-1.24	P<0.05	25
1	2922	910.37	34.12	2	1819.73	EGTCPEAPTDECKPVK	-1.25	P<0.05	19
1	2053	607.24	34.11	3	1819.70	EGTCPEAPTDECKPVK	-1.25	P<0.001	19
1	905	442.21	37.46	3	1324.61	KDSGFQMNQLR	-1.26	P<0.05	18
1	3271	489.23	58.13	4	1953.90	NLNEKDYELLCLDGTR	-1.26	P<0.05	23
1	2247	641.26	43.62	2	1281.51	CDEWSVNSVGK	-1.26	P<0.005	17
1	744	425.54	47.59	3	1274.60	HSTIFENLANK	-1.27	P<0.005	16
1	4461	652.30	61.93	3	1954.88	NLNEKDYELLCLDGTR	-1.27	P<0.05	23
1	1400	508.56	46.07	3	1523.66	LKCDEWSVNSVGK	-1.28	P<0.005	33
1	3036	1036.94	60.74	2	2072.87	SDNCEDTPEAGYFAVAVVK	-1.29	P<0.05	24
1	2378	678.29	60.45	2	1355.57	DYELLCLDGTR	-1.29	P<0.005	15
1	4046	992.42	69.61	3	2975.24	LCMGSGLNLCEPNNKEGYYGYTGAFR	-1.30	P<0.05	14
1	2806	827.39	30.57	1	827.39	NPDPWAK	-1.32	P<0.05	21
1	997	452.53	60.45	3	1355.57	DYELLCLDGTR	-1.32	P<0.001	15
1	2693	770.83	59.06	2	1540.65	DQYELLCLDNTR	-1.33	P<0.001	13
1	1436	514.22	59.06	3	1540.64	DQYELLCLDNTR	-1.37	P<0.001	13
1	2092	613.81	54.09	2	1226.61	SLDGGFVYIAGK	-1.38	P<0.001	12
1	1812	569.57	48.82	3	1706.69	FDEFFSEGC*APGSKK	-1.39	P<0.05	26
1	2166	628.27	54.36	3	1882.79	ADRDQYELLCLDNTR	-1.40	P<0.001	11
1	3963	898.46	55.62	1	898.46	SKEFQLF	-1.40	P<0.05	10
1	2962	941.91	54.32	2	1882.81	ADRDQYELLCLDNTR	-1.43	P<0.005	11
1	1138	471.46	54.37	4	1882.82	ADRDQYELLCLDNTR	-1.43	P<0.001	11
1	1868	576.25	43.29	2	1151.49	LKCDEWSVN	-1.44	P<0.001	9
1	622	409.54	54.10	3	1226.60	SLDGGFVYIAGK	-1.44	P<0.01	12
1	3353	530.24	35.82	3	1588.70	KPVEEYANCHLAR	-1.45	P<0.01	8
1	3035	1035.50	90.27	2	2069.99	EDLIWELLNQAQEHFGK	-1.50	P<0.05	7
1	745	425.55	43.73	3	1274.63	HSTIFENLANK	-1.54	P<0.01	16
1	2295	652.34	83.60	2	1303.67	SAGWNIPIGLLY	-1.58	P<0.005	6
1	1022	456.75	39.14	2	912.49	YYAVAVVK	-1.63	P<0.005	5
1	1903	582.26	46.01	2	1163.51	LYCDLPEPR	-1.64	P<0.001	4
1	2577	732.70	66.92	3	2196.08	DAYLAPNNLKPVVAEFYGSK	-1.66	P<0.001	3
1	977	449.73	55.53	2	898.45	SKEFQLF	-1.70	P<0.001	10
1	2103	616.33	58.44	3	1846.97	LAPNNLKPVVAEFYGSK	-1.96	P<0.005	2
1	1871	576.57	46.47	3	1727.69	IECVSAETTEDCIAK	-3.06	P<0.01	1
2	2144	625.28	50.38	2	1249.55	LGMFNIQHCK	-1.15	P<0.05	39
2	678	417.20	50.38	3	1249.58	LGMFNIQHCK	-1.18	P<0.005	39

3	4494	720.78	38.34	2	1440.55	TEGDGVYTLNNEK	-1.17	CountDiff	41
3	1054	460.70	32.50	2	920.39	GSFPWQAK	-1.18	P<0.05	40
4	3973	905.44	85.21	3	2714.30	HYYIAAEEIIWNYAPSGIDIFTK	-1.01	CountDiff	43
4	4732	1191.63	70.02	1	1191.63	DIFTGLIGPMK	-1.03	CountDiff	42
4	536	397.87	70.00	3	1191.59	DIFTGLIGPMK	-1.13	CountDiff	42
5	2106	616.95	66.74	3	1848.83	QFSFPLSSEPFQGSYK	-1.15	P<0.01	63
5	1722	558.27	62.48	3	1672.79	TEHPFTVEEFVLPK	-1.21	P<0.05	62
5	2093	614.26	44.57	2	1227.51	YDVENCLANK	-1.23	P<0.05	61
5	2679	765.34	20.66	2	1529.67	TAQEGDHGSHVYTK	-1.24	P<0.05	60
5	1681	550.28	51.89	2	1099.55	QTVSWAVTPK	-1.24	P<0.05	59
5	3176	409.86	41.19	3	1227.56	YDVENCLANK	-1.25	P<0.05	61
5	581	403.70	22.11	2	806.39	GPTQEFK	-1.25	P<0.05	58
5	1739	559.70	33.80	4	2235.78	KYSDASDCHGEDSQAFCEK	-1.26	P<0.05	57
5	2470	703.24	36.04	3	2107.70	YSDASDC*HGEDSQAFC*EK	-1.26	P<0.05	56
5	2848	848.77	63.56	3	2544.29	SVSGKPQYMVLVPSLLHTETTEK	-1.26	P<0.05	55
5	2964	942.51	67.49	2	1884.01	VSVQLEASPAFLAVPVEK	-1.26	P<0.05	54
5	2854	850.35	64.42	3	2549.03	VYDYYETDEFAIAEYNAPCSK	-1.27	P<0.05	53
5	2623	745.94	33.80	3	2235.80	KYSDASDCHGEDSQAFCEK	-1.27	P<0.05	57
5	1629	540.94	29.92	3	1620.80	DNSVHWERPQKPK	-1.28	P<0.005	52
5	1687	552.29	41.86	2	1103.57	SSGSLLNNAIK	-1.29	P<0.05	51
5	3099	1226.53	42.46	1	1226.53	YDVENC*LANK	-1.29	P<0.05	50
5	2701	773.39	34.13	2	1545.77	LVHVEEPHTETVR	-1.31	P<0.01	49
5	460	387.19	34.13	4	1545.74	LVHVEEPHTETVR	-1.34	CountDiff	49
5	2358	671.85	47.89	2	1342.69	AVLPTGDVIGDSAK	-1.36	P<0.05	48
5	2884	872.79	72.26	3	2616.35	VLLAYLTAQPAPTSEDLTSATNIVK	-1.40	P<0.05	47
5	1452	515.93	34.11	3	1545.77	LVHVEEPHTETVR	-1.46	P<0.005	49
5	1486	519.48	54.00	4	2074.90	MCPQLQQYEMHGPEGLR	-1.47	P<0.05	46
5	2428	692.63	54.84	3	2075.87	MCPQLQQYEMHGPEGLR	-1.63	P<0.001	46
5	3063	1103.60	41.87	1	1103.60	SSGSLLNNAIK	-1.69	P<0.005	51
5	1435	513.79	43.84	2	1026.57	TVLQDVPVR	-2.05	P<0.001	45
5	3447	587.33	55.43	2	1173.65	FTVLQDVPVR	-2.08	P<0.05	44
6	1470	518.26	70.75	3	1552.76	RHPYFYAPELLF	-1.02	CountDiff	85
6	3722	722.81	36.79	2	1444.61	YICENQDSISSK	-1.05	CountDiff	84
6	3387	555.56	42.99	3	1664.66	YKAAFTEC*C*QAADK	-1.09	CountDiff	83
6	1858	575.28	46.40	2	1149.55	LVNEVTEFAK	-1.13	P<0.01	82
6	2357	671.79	66.50	2	1342.57	AVMDDFAAFVEK	-1.15	P<0.05	81

6	160	337.18	29.16	2	673.35	AWAVAR	-1.15	P<0.05	80
6	92	323.17	24.20	2	645.33	LDELR	-1.15	P<0.05	79
6	2389	682.34	69.00	3	2045.00	VFDEFKPLVEEPQNLIK	-1.18	P<0.005	78
6	1353	500.84	29.65	3	1500.50	ADDKETCFAEEGK	-1.18	P<0.05	77
6	1664	547.29	49.10	3	1639.85	KVPQVSTPTLVEVSR	-1.19	P<0.05	76
6	1823	570.72	36.08	2	1140.43	CCTESLVNR	-1.19	P<0.05	75
6	1425	512.02	69.00	4	2045.06	VFDEFKPLVEEPQNLIK	-1.19	P<0.05	78
6	1277	489.94	55.46	3	1467.80	RHPDYSVVLLLR	-1.22	P<0.005	74
6	3618	663.80	67.08	4	2652.18	LVRPEVDVMCTAFHDNEETFLK	-1.24	CountDiff	73
6	1866	575.79	44.55	2	1150.57	LVNEVTEFAK	-1.25	P<0.05	82
6	1187	476.69	37.88	2	952.37	DLGEENFK	-1.25	P<0.05	72
6	1031	458.51	37.01	3	1373.51	AAFTECCQAADK	-1.27	P<0.05	71
6	3031	1023.03	69.00	2	2045.05	VFDEFKPLVEEPQNLIK	-1.29	P<0.05	78
6	4029	967.00	63.89	2	1932.99	SLHTLFGDKLCTVATLR	-1.31	P<0.05	70
6	2406	687.25	37.01	2	1373.49	AAFTECCQAADK	-1.31	P<0.005	71
6	1377	504.61	52.37	3	1511.81	VPQVSTPTLVEVSR	-1.33	P<0.01	69
6	4078	1045.39	43.22	2	2089.77	VHTECCHGDLLECADDR	-1.36	P<0.05	68
6	1300	492.73	29.96	2	984.45	TYETTLEK	-1.36	P<0.005	67
6	2980	956.44	58.81	2	1911.87	RPCFSALEVDETYVPK	-1.36	P<0.05	66
6	1199	478.72	58.77	4	1911.86	RPCFSALEVDETYVPK	-1.37	P<0.05	66
6	2998	984.48	29.93	1	984.48	TYETTLEK	-1.41	P<0.05	67
6	2234	637.96	58.76	3	1911.86	RPCFSALEVDETYVPK	-1.42	P<0.005	66
6	1514	523.19	43.22	4	2089.74	VHTECCHGDLLECADDR	-1.48	P<0.001	68
6	2447	697.25	43.22	3	2089.73	VHTECCHGDLLECADDR	-1.48	P<0.001	69
6	969	449.24	78.58	3	1345.70	FYAPELLFFAK	-1.64	P<0.05	65
6	1115	469.24	60.31	3	1405.70	RHPYFYAPELL	-1.66	P<0.001	64
8	2027	602.28	57.48	3	1804.82	AEDHFSVIDFNQNIR	-1.20	P<0.05	96
8	528	396.71	24.94	2	792.41	ALYAQAR	-1.25	P<0.05	95
8	1922	585.26	47.58	2	1169.51	SSALDMENFR	-1.27	P<0.05	94
8	2486	708.03	62.77	3	2122.07	VVNNSPQPQNVVFDVQIPK	-1.27	P<0.05	93
8	732	423.74	32.33	2	846.47	IYLQPGR	-1.29	P<0.01	92
8	2745	791.92	49.76	2	1582.83	IQPSGGTNINEALLR	-1.31	P<0.05	91
8	338	367.94	31.40	4	1468.74	AHVSFKPTVAQQR	-1.32	P<0.05	90
8	945	446.24	22.46	2	891.47	VQSTITSR	-1.35	P<0.005	89
8	1551	528.28	49.74	3	1582.82	IQPSGGTNINEALLR	-1.35	P<0.005	91
8	649	413.53	23.04	3	1238.57	LSNENHGIAQR	-1.36	P<0.01	88

8	1278	490.26	31.39	3	1468.76	AHVSFKPTVAQQR	-1.37	P<0.01	90
8	728	423.23	50.80	2	845.45	TILDDLR	-1.43	P<0.001	87
8	1440	514.28	37.68	2	1027.55	TEVNVLPGAK	-1.46	P<0.005	86
10	1896	580.80	61.15	2	1160.59	WFYIASAFR	-1.23	P<0.05	97
11	2225	636.82	63.64	4	2544.26	GFYPSDIAVEWESNGQPENNYK	-1.38	P<0.005	98
11	2227	636.99	63.94	4	2544.94	GFYPSDIAVEWESNGQPENNYK	-16.67	P<0.05	98
12	2603	740.33	48.76	2	1479.65	GTFATLSELHCDK	-1.14	CountDiff	105
12	1050	460.23	45.99	3	1378.67	EFTPPVQAAYQK	-1.18	P<0.05	104
12	3032	1029.96	68.32	2	2058.91	FFESFGDLSTPDAVMGNPK	-1.39	P<0.05	103
12	2270	647.55	62.52	4	2587.18	GTFATLSELHC*DKLHVDPENFR	-1.51	P<0.05	102
12	2419	689.84	43.49	2	1378.67	EFTPPVQAAYQK	-1.52	P<0.01	104
12	2405	686.97	68.34	3	2058.89	FFESFGDLSTPDAVMGNPK	-1.60	P<0.005	103
12	878	438.88	46.08	3	1314.62	VNVDEVGGEALGR	-1.71	P<0.05	101
12	2233	637.85	62.18	2	1274.69	LLVVYPWTQR	-1.76	P<0.005	100
12	438	383.88	36.67	3	1149.62	VVAGVANALAHK	-1.77	P<0.05	99
12	2319	657.82	46.12	2	1314.63	VNVDEVGGEALGR	-1.92	P<0.001	101
12	1308	493.89	48.78	3	1479.65	GTFATLSELHCDK	-2.12	P<0.005	105
13	866	437.71	27.44	2	874.41	QLANGVDR	-1.15	P<0.05	107
13	863	437.24	28.51	2	873.47	QLANGVDR	-1.23	P<0.05	107
13	325	365.70	26.66	2	730.39	TLDPER	-1.33	P<0.05	106
15	3507	616.96	75.84	3	1848.86	EQLQDMGLVDLFSPEK	-1.24	P<0.05	112
15	799	430.74	46.11	2	860.47	LQPLDFK	-1.25	P<0.05	111
15	3595	655.30	46.04	2	1309.59	DDLYVSDAFHK	-1.26	P<0.05	110
15	1410	510.24	50.55	3	1528.70	FATTFYQHLADSK	-1.27	P<0.05	109
15	858	437.20	46.05	3	1309.58	DDLYVSDAFHK	-1.43	P<0.01	110
15	3700	705.81	62.07	2	1410.61	DIPMNPMC*IYR	-1.47	P<0.005	108
16	1933	587.28	43.64	5	2932.37	FVSEAGPTGTGESKCPLMVKVLDAVRGSP	-1.08	CountDiff	117
16	3502	614.53	67.64	4	2455.10	TSESGELHGLTTEEEFVEGIYK	-1.16	P<0.05	116
16	1019	456.24	53.99	3	1366.70	GSPAINVAVHVFR	-1.26	P<0.05	115
16	4169	1394.68	47.33	1	1394.68	AADDTWEPFASGK	-1.32	P<0.05	114
16	2397	683.87	54.00	2	1366.73	GSPAINVAVHVFR	-1.33	P<0.01	115
16	2450	697.80	50.88	2	1394.59	AADDTWEPFASGK	-1.35	P<0.01	114
16	3499	613.80	58.28	4	2452.18	ALGISPFHEHAEVVFTANDSGPR	-1.38	P<0.01	113
17	1203	479.71	24.31	2	958.41	HADPDFTR	-1.15	P<0.05	121
17	1311	494.58	28.67	3	1481.72	IYGNQDTSSQLKK	-1.24	P<0.05	120
17	3849	797.33	53.74	3	2389.97	MLADAPPQDPSC*C*SGALYYGSK	-1.25	P<0.05	119

17	2375	677.33	31.71	2	1353.65	IYGNQDTSSQLK	-1.45	P<0.005	118
18	4799	735.95	57.96	3	2205.83	MHSMNGFMYGNQPGLTMC*K	-1.09	CountDiff	122
19	4464	653.27	39.62	2	1305.53	GQYC*YELDEK	-1.26	CountDiff	124
19	1170	474.88	46.42	3	1422.62	FEDGVLDPDYPR	-1.41	P<0.05	123
20	261	354.20	29.67	2	707.39	ANLFNK	-1.40	P<0.05	125
20	2483	707.40	29.66	1	707.40	ANLFNK	-1.42	P<0.05	125
24	1698	554.29	61.79	4	2214.14	DKLAAC*LEGNC*AEGLGTNYR	-1.16	P<0.05	127
24	1255	486.74	25.94	2	972.47	YTACETAR	-1.44	P<0.05	126
25	2634	749.85	76.06	4	2996.38	VADALTNAVAHVDDMPNALSALSDLHAHK	-1.38	P<0.05	130
25	2148	625.71	74.52	5	3124.52	KVADALTNAVAHVDDMPNALSALSDLHAHK	-1.48	P<0.05	129
25	2012	600.08	76.07	5	2996.37	VADALTNAVAHVDDMPNALSALSDLHAHK	-1.66	P<0.05	130
25	1414	510.57	37.39	3	1529.69	VGAHAGEYGAEALER	-2.03	P<0.01	128
26	2102	615.85	71.57	2	1230.69	QGLLPVLESFK	-1.29	P<0.05	132
26	1602	538.25	64.78	3	1612.73	LLDNWDSVTSTFSK	-1.48	P<0.05	131
27	4121	1159.05	74.07	2	2317.09	QSNNKYAASSYLSLTPEQWK	-1.09	CountDiff	133
28	3681	695.36	58.09	3	2084.06	LQQVLHAGSGPCLPHLLSR	-1.15	P<0.05	134
30	1758	561.77	46.26	2	1122.53	QVEGMEDWK	-1.54	P<0.005	135
32	378	375.22	32.72	2	749.43	MLSLGTK	-1.66	P<0.001	137
33	321	365.20	21.50	2	729.39	ATGIPDR	-1.87	P<0.05	138
34	3454	589.55	33.80	3	1766.63	EEEQQRCESLAEVNT	-1.68	P<0.05	139
34	4248	442.41	33.78	4	1766.62	EEEQQRCESLAEVNT	-1.80	P<0.05	139
35	2568	727.88	67.66	2	1454.75	MNQLTQELFSLK	-1.55	P<0.01	140
38	4762	693.90	62.09	2	1386.79	NVPLPVIAELPPK	-1.22	CountDiff	142
38	807	431.73	29.49	2	862.45	VTSTLTIK	-3.58	CountDiff	141
40	2977	953.43	68.34	2	1905.85	TTPPMLDSDGSFFLYSK	-1.38	P<0.05	144
40	2001	598.98	69.85	3	1794.92	VVSVLTVVHQDWLNGK	-1.46	CountDiff	143
40	2221	635.99	67.72	3	1905.95	TTPPMLDSDGSFFLYSK	-1.64	P<0.05	144
42	1908	582.74	39.88	2	1164.47	LPECEAVCGK	-5.08	CountDiff	145
51	1431	513.00	52.30	4	2048.98	RLYGSEAFATDFQDSAAAK	-1.15	P<0.05	146
52	1702	554.57	53.77	3	1661.69	EHAVEGDCDFQLLK	-1.28	P<0.005	147
53	2625	746.29	48.62	3	2236.85	KEDSC*QLGYSAGPC*MGMTSR	-1.33	P<0.05	148
54	1137	471.28	43.44	2	941.55	EQLTPLIK	-1.44	P<0.05	149
56	553	400.50	25.61	3	1199.48	EQHPDMSVTR	-1.26	P<0.05	150
57	3610	660.32	50.55	2	1319.63	AGALNSNDAFVLK	-7.09	P<0.01	151
59	2343	668.66	68.53	3	2003.96	GSLVQASEANLQAAQDFVR	-1.19	P<0.05	152
60	1585	534.20	53.42	3	1600.58	IASFSQNC*DIYPGK	-1.21	P<0.05	153

61	2933	921.35	60.09	4	3682.38	CGLVPVLAENYKSQQSSDPDPNCVDRPVEGYLA	-1.28	P<0.05	154
62	829	433.23	40.61	3	1297.67	SLEDLQLTHNK	-1.02	CountDiff	156
62	2088	613.30	50.92	2	1225.59	ISNIPDEYFK	-1.55	P<0.001	155
66	931	445.21	60.18	2	889.41	QNGGLATVE	-1.54	P<0.005	157
70	1614	539.25	72.38	3	1615.73	M#C*EQALGKGC*GGDSK	-1.31	P<0.005	158
71	3662	689.69	69.01	3	2067.05	LLNLDGTC*ADSYSFVFSR	-1.34	P<0.001	159
72	1729	558.79	42.03	2	1116.57	AGKSTFLKKH	-1.21	P<0.01	160
72	3069	1116.60	42.02	1	1116.60	AGKSTFLKKH	-1.32	P<0.05	160
74	4442	634.61	49.49	3	1901.81	EIVMTQSPATLSVSPGER	-1.26	P<0.05	161
75	3442	586.29	46.40	2	1171.57	EGLCCGPSIPPV	-1.20	P<0.05	162
79	1350	500.72	42.14	2	1000.43	AAYMNKER	-1.18	P<0.01	163
79	3015	1000.48	42.14	1	1000.48	AAYMNKER	-1.22	P<0.05	163
81	1342	499.55	58.16	3	1496.63	YYCFQGNQFLR	-1.23	P<0.05	164
82	1103	467.88	38.36	3	1401.62	GGCLPPC*DGGPKSR	-1.35	P<0.05	165
86	4438	632.30	61.38	2	1263.59	ASDDDVGENARI	-1.17	P<0.05	166
88	4067	1019.60	54.28	1	1019.60	EEAIAVTMR	-1.27	P<0.05	167
91	1495	520.91	39.58	3	1560.71	YNPDSGLEVLAVQR	-1.45	P<0.05	168
95	4751	400.56	53.85	3	1199.66	IVDLVKELDR	-1.29	CountDiff	169
99	3280	494.73	36.75	4	1975.90	HKLIHTGVKSHACEQCGK	-1.19	P<0.05	170
103	3639	671.30	61.56	3	2011.88	VFWRSSGLPHPSQAQSAR	-1.20	P<0.05	171
105	3190	420.21	49.15	4	1677.82	GNALSVC*SRESPGSKK	-1.22	P<0.05	172
110	3018	1000.93	62.13	4	4000.70	CLQRIVTKLQMEAGLCEEQLNQADALLQSDVRL-LAA	-1.22	CountDiff	173
110	4159	1334.21	62.14	3	4000.61	CLQRIVTKLQMEAGLCEEQLNQADALLQSDVRL-LAA	-1.44	CountDiff	173
111	2673	762.06	67.89	3	2284.16	IITHPNFNGNTLDNDIMLIK	-1.09	CountDiff	174
112	1269	489.00	72.92	4	1952.98	FTVDRPFLFLIYEHR	-1.06	CountDiff	175
113	4790	502.25	42.95	2	1003.49	GGSIFGLAPGK	-1.28	CountDiff	176
114	1429	512.78	45.54	2	1024.55	GQGKPPVWR	-1.17	CountDiff	177
3†	4777	1145.50	50.05	3	3434.48	AVGDKLPECEADDGCPKPPEIAHGYVEHSVR	NA	CountDiff	178

†Trend was neutral rather than decreased

Table 5. Unidentified Proteins Increased in Subjects having RA

Component #	m/z	R.T.(min.)	z	M+H	Fold Change	P
1929	585.94	56.22	3	1755.8	1.01	CountDiff
1129	470.7	39.77	2	940.39	1.02	CountDiff
3401	561.79	52.59	2	1122.57	1.02	CountDiff
423	382.54	35.58	3	1145.6	1.02	CountDiff
4779	362.87	40.15	3	1086.59	1.03	CountDiff
171	339.71	12.84	2	678.41	1.04	CountDiff
150	335.68	25.8	1	335.68	1.04	CountDiff
225	349.18	29.85	2	697.35	1.04	CountDiff
3864	805.48	51.64	1	805.48	1.05	CountDiff
2403	686.64	54.04	3	2057.9	1.05	CountDiff
4200	371.46	14.54	3	1112.36	1.06	CountDiff
3982	910.07	26.24	4	3637.26	1.06	CountDiff
54	314.22	42.28	2	627.43	1.07	P<0.05
4667	633.32	61.28	1	633.32	1.07	CountDiff
1303	493.2	35.92	3	1477.58	1.09	CountDiff
4597	625.32	22.97	1	625.32	1.09	CountDiff
3954	883.38	73.84	2	1765.75	1.09	CountDiff
547	399.85	24.21	3	1197.53	1.09	CountDiff
1428	512.6	66.52	3	1535.78	1.1	CountDiff
4691	1152.25	84.26	4	4605.98	1.1	CountDiff
4104	1089.98	96.74	5	5445.87	1.1	CountDiff
4211	398.2	37.52	2	795.39	1.11	P<0.05
4087	1062.43	48.57	1	1062.43	1.12	CountDiff
1457	516.26	23.89	1	516.26	1.12	CountDiff
3344	527.27	54.34	2	1053.53	1.13	P<0.05
1055	460.71	44.94	2	920.41	1.15	P<0.05
3659	686.97	53.57	3	2058.89	1.15	CountDiff
1754	561.26	80.75	3	1681.76	1.16	P<0.05
219	347.71	31.81	2	694.41	1.17	P<0.05
1235	483.74	34.29	2	966.47	1.17	CountDiff
974	449.54	51.44	3	1346.6	1.17	CountDiff
1227	482.26	39.67	2	963.51	1.17	CountDiff
4776	1093.82	57.68	3	3279.44	1.17	NA
1627	540.81	64.79	1	540.81	1.18	P<0.005
4697	565.26	54.05	1	565.26	1.18	CountDiff
165	339.2	54.33	3	1015.58	1.19	P<0.005
1939	588.91	52.16	3	1764.71	1.19	P<0.05
2408	687.43	31.01	1	687.43	1.19	P<0.05
1549	527.8	54.48	2	1054.59	1.19	P<0.05
4614	717.34	58.75	2	1433.67	1.19	CountDiff
788	429.73	35.02	2	858.45	1.2	P<0.05
717	422.22	23.02	2	843.43	1.2	P<0.05
3354	530.3	54.32	2	1059.59	1.2	P<0.05
4083	1057.41	49.26	4	4226.62	1.2	P<0.05
3157	382.22	33.47	2	763.43	1.21	P<0.05

205	344.91	40.1	5	1720.52	1.22	P<0.01
36	309.68	26.8	2	618.35	1.22	P<0.05
1111	468.74	33.42	2	936.47	1.22	P<0.05
2658	755.34	80.21	2	1509.67	1.22	CountDiff
4634	984.81	84.96	5	4920.02	1.22	CountDiff
3413	566.78	50.07	2	1132.55	1.23	P<0.005
1313	495.21	57.34	3	1483.61	1.23	P<0.05
131	332.15	29.8	2	663.29	1.23	P<0.05
3173	404.7	39.1	2	808.39	1.23	CountDiff
880	438.97	56.3	4	1752.86	1.24	P<0.01
3462	594.57	73.89	3	1781.69	1.24	P<0.05
890	440.2	47.63	2	879.39	1.24	P<0.05
164	338.7	11.4	2	676.39	1.24	P<0.05
4770	832.47	54.81	1	832.47	1.24	NA
1492	520.34	29.2	1	520.34	1.25	P<0.05
850	436.19	50.2	3	1306.55	1.25	P<0.05
1801	567.8	71.05	2	1134.59	1.25	P<0.05
2916	902.47	50.72	2	1803.93	1.26	P<0.05
1568	531.75	35.37	2	1062.49	1.26	P<0.05
2124	621.29	42.93	2	1241.57	1.27	P<0.05
3757	741.59	56.7	4	2963.34	1.27	CountDiff
203	344.68	25.84	2	688.35	1.28	P<0.005
3464	596.29	27.57	2	1191.57	1.28	P<0.005
3024	1015.6	54.32	1	1015.6	1.28	P<0.01
1943	589.25	73.91	3	1765.73	1.28	P<0.01
363	372.69	29.26	2	744.37	1.28	P<0.05
2759	800.73	62.02	5	3999.62	1.28	P<0.05
2067	609.32	30.2	1	609.32	1.28	P<0.05
2402	686.43	34.29	1	686.43	1.29	P<0.001
1920	584.97	56.3	3	1752.89	1.29	P<0.005
275	357.19	33.78	3	1069.55	1.29	P<0.005
2373	676.83	64.5	2	1352.65	1.29	P<0.05
1228	482.27	53.95	2	963.53	1.31	P<0.01
2203	633.77	43.97	4	2532.06	1.31	P<0.01
3135	328.22	10.99	2	655.43	1.31	P<0.05
1966	593.8	48.43	2	1186.59	1.31	P<0.05
385	376.84	22.69	3	1128.5	1.31	P<0.05
3495	613.31	70.94	2	1225.61	1.32	P<0.005
1263	488.23	33.94	3	1462.67	1.32	P<0.01
505	393.21	18.66	2	785.41	1.32	P<0.01
831	433.23	37.51	2	865.45	1.32	P<0.05
1590	535.28	12.37	1	535.28	1.32	P<0.05
810	431.81	42.24	4	1724.22	1.32	P<0.05
2431	693.85	47.78	2	1386.69	1.33	P<0.01
2439	695.31	37.12	2	1389.61	1.33	P<0.01
4649	485.24	50.32	2	969.47	1.33	P<0.05
4569	411.2	38.23	1	411.2	1.33	P<0.05
1725	558.5	53.76	4	2230.98	1.33	P<0.05

4702	622.99	78.35	3	1866.95	1.33	CountDiff
984	450.72	37.19	2	900.43	1.34	P<0.05
4469	671.36	35.72	1	671.36	1.34	P<0.05
4679	758.83	55.08	4	3032.3	1.35	P<0.05
4654	525.73	54.66	5	2624.62	1.35	CountDiff
3	300.17	12.05	2	599.33	1.36	P<0.01
3607	659.82	64.34	4	2636.26	1.36	P<0.05
1162	473.75	41.42	2	946.49	1.36	P<0.05
2721	785.44	18.65	1	785.44	1.37	P<0.01
4600	633.8	60.37	1	633.8	1.37	P<0.05
1705	555.8	54.27	2	1110.59	1.38	P<0.001
330	366.2	27.4	2	731.39	1.38	P<0.005
118	329.17	31.91	2	657.33	1.38	P<0.05
1946	589.59	52.25	3	1766.75	1.38	P<0.05
3394	557.26	71.31	3	1669.76	1.38	CountDiff
3371	542.24	60.8	3	1624.7	1.39	P<0.001
433	383.52	44.97	3	1148.54	1.39	P<0.005
4032	973.52	45.19	1	973.52	1.39	P<0.05
720	422.23	25.64	2	843.45	1.39	P<0.05
1569	532	53.75	4	2124.98	1.39	P<0.05
4633	978.46	50.37	1	978.46	1.39	CountDiff
2723	785.92	66.44	2	1570.83	1.4	P<0.005
88	322.18	29.89	3	964.52	1.4	P<0.01
4237	426.21	35.62	1	426.21	1.41	P<0.001
2457	699.34	62.69	1	699.34	1.41	P<0.05
1733	559.4	53.2	5	2792.97	1.41	P<0.05
1704	555.78	50.1	2	1110.55	1.42	P<0.001
48	312.83	33.43	3	936.47	1.42	P<0.005
4323	511.28	22.86	2	1021.55	1.42	P<0.05
1565	531.28	52.2	2	1061.55	1.43	P<0.005
400	379.72	27.31	2	758.43	1.43	P<0.005
1727	558.73	21.44	2	1116.45	1.43	P<0.005
2368	674.85	64.55	2	1348.69	1.43	P<0.005
3342	526.22	28.38	3	1576.64	1.43	P<0.05
3541	630.96	62.7	3	1890.86	1.43	P<0.05
4757	567.25	92.73	4	2265.98	1.43	CountDiff
4007	940.16	74.57	4	3757.62	1.44	P<0.05
1571	532.26	48.01	3	1594.76	1.45	P<0.01
828	433.23	40.32	2	865.45	1.45	P<0.05
2136	624.32	51.59	3	1870.94	1.45	P<0.05
2982	960.09	35.93	3	2878.25	1.45	CountDiff
4659	563.26	38.51	2	1125.51	1.45	CountDiff
1694	553.69	50.84	2	1106.37	1.45	CountDiff
4719	858.75	71.63	1	858.75	1.45	NA
695	419.2	27.39	2	837.39	1.46	P<0.005
3518	623.32	51.82	3	1867.94	1.46	P<0.05
132	332.15	16.33	2	663.29	1.46	P<0.05
4642	1117.49	82.35	4	4466.94	1.46	P<0.05

2949	932.52	48.7	1	932.52	1.46	CountDiff
327	366.16	39.18	3	1096.46	1.47	P<0.01
1260	487.28	54.08	3	1459.82	1.47	P<0.05
2130	622.82	53.25	2	1244.63	1.47	P<0.05
4378	572.84	61.44	5	2860.17	1.47	P<0.05
2886	876.96	56.3	2	1752.91	1.48	P<0.005
2633	749.33	39.73	2	1497.65	1.48	CountDiff
2725	786.37	59.71	1	786.37	1.49	P<0.005
2932	920.45	44.92	1	920.45	1.49	P<0.005
2317	657.35	31.91	1	657.35	1.49	P<0.005
2618	744.34	53.76	3	2231	1.49	P<0.01
1074	463.58	47.03	5	2313.87	1.49	P<0.01
3459	593.49	56.69	5	2963.42	1.49	P<0.05
356	370.86	50.12	3	1110.56	1.5	P<0.001
2697	772.04	46.84	3	2314.1	1.5	P<0.001
4086	1061.58	52.2	1	1061.58	1.5	P<0.001
3852	799.11	66.21	4	3193.42	1.5	P<0.005
4524	852.86	55.21	4	3408.42	1.5	P<0.05
2171	628.71	51.69	1	628.71	1.5	P<0.05
3434	579.78	75.84	4	2316.1	1.5	P<0.05
80	319.68	48.65	4	1275.7	1.5	P<0.05
1258	487.26	45.19	2	973.51	1.51	P<0.001
2033	602.98	49.55	3	1806.92	1.51	P<0.005
1163	473.75	40.24	2	946.49	1.51	P<0.005
3068	1116.01	53.76	2	2231.01	1.51	P<0.01
2818	835.39	71.39	4	3338.54	1.51	P<0.05
4122	1162.85	73.85	3	3486.53	1.51	P<0.05
1276	489.73	50.37	2	978.45	1.51	P<0.05
2391	682.49	55.25	5	3408.42	1.52	P<0.05
365	372.72	40.29	1	372.72	1.52	P<0.05
2592	738.79	55.32	2	1476.57	1.53	P<0.05
3832	787.87	54.62	4	3148.46	1.53	P<0.05
4782	589.83	31.56	2	1178.65	1.53	CountDiff
1248	485.25	49.14	2	969.49	1.54	P<0.001
4123	1163.49	64.07	4	4650.94	1.54	P<0.005
823	432.74	35.99	2	864.47	1.54	P<0.01
3366	536.74	98.24	4	2143.94	1.54	P<0.05
218	347.68	26.64	2	694.35	1.55	P<0.05
3001	989.19	66.15	5	4941.92	1.55	P<0.05
331	366.41	46.86	4	1462.62	1.55	P<0.05
4632	930.97	64.08	5	4650.82	1.55	P<0.05
531	397.2	34.11	2	793.39	1.56	P<0.05
1301	492.88	55.24	3	1476.62	1.57	P<0.05
3649	680.08	81.09	4	2717.3	1.57	P<0.05
930	444.87	22.84	3	1332.59	1.57	P<0.05
4608	671.3	54.62	1	671.3	1.57	CountDiff
3726	725.33	57.49	1	725.33	1.58	P<0.001
4	300.7	26.26	2	600.39	1.58	P<0.005

563	401.49	39.18	3	1202.45	1.58	P<0.01
1537	526.29	62.08	3	1576.85	1.58	P<0.01
2411	688.37	25.86	1	688.37	1.59	P<0.001
1732	559.25	53.19	5	2792.22	1.59	P<0.05
1697	554.26	52.23	3	1660.76	1.59	P<0.05
2676	763.09	52.63	4	3049.34	1.6	P<0.005
114	328.2	31.63	1	328.2	1.6	P<0.05
1119	469.72	31.01	2	938.43	1.6	P<0.05
3224	456.25	23.34	2	911.49	1.6	CountDiff
992	451.98	49.51	4	1804.9	1.61	P<0.001
2894	883.89	52.24	2	1766.77	1.61	P<0.05
3435	579.78	73.1	4	2316.1	1.61	P<0.05
1848	573.57	50.13	5	2863.82	1.62	P<0.001
4259	455.53	41.8	3	1364.57	1.62	P<0.001
1316	495.27	40.48	2	989.53	1.62	P<0.001
3129	311.19	33.16	2	621.37	1.62	P<0.005
2356	671.34	38.28	1	671.34	1.62	P<0.005
2435	694.34	58.61	3	2081	1.62	P<0.01
3186	417.21	36.27	2	833.41	1.63	P<0.001
2024	601.75	39.19	2	1202.49	1.63	P<0.005
3650	680.08	82.94	4	2717.3	1.63	P<0.005
3084	1148.98	64.5	4	4592.9	1.63	P<0.005
3182	415.24	16	2	829.47	1.63	P<0.01
1302	492.94	57.64	3	1476.8	1.63	P<0.05
1971	594.06	48.62	1	594.06	1.63	P<0.05
152	336.17	38.28	2	671.33	1.64	P<0.005
3859	800.94	62.17	4	3200.74	1.64	CountDiff
1706	555.8	52.58	2	1110.59	1.65	P<0.001
4228	418.72	27.67	1	418.72	1.65	P<0.05
281	358.71	34.21	2	716.41	1.66	P<0.001
2930	919.39	64.5	5	4592.92	1.66	P<0.005
4664	608.94	54.61	3	1824.8	1.66	P<0.05
722	423.02	30.9	1	423.02	1.67	P<0.001
2073	610.66	52.64	5	3049.27	1.67	P<0.005
3215	444.27	40.66	1	444.27	1.67	P<0.01
4318	508.47	39.22	4	2030.86	1.67	CountDiff
4708	645.8	46.29	4	2580.18	1.67	CountDiff
2948	932.18	64.43	5	4656.87	1.7	P<0.05
1885	579.28	46.85	4	2314.1	1.71	P<0.001
2286	650.81	27.69	2	1300.61	1.71	P<0.001
3892	826.39	73.75	2	1651.77	1.71	P<0.01
3951	878.67	26.95	3	2633.99	1.71	P<0.05
411	381.18	24.76	2	761.35	1.71	P<0.05
4307	493.95	49.84	4	1972.78	1.71	CountDiff
2763	802.75	48.73	3	2406.23	1.72	P<0.005
4475	681.51	73.68	4	2723.02	1.72	P<0.05
1033	458.74	39.69	2	916.47	1.72	P<0.05
2866	858.48	35.02	1	858.48	1.74	P<0.001

4575	442.72	39.02	4	1767.86	1.75	P<0.01
4295	484.76	46.41	2	968.51	1.76	P<0.05
3566	639.49	66.22	5	3193.42	1.77	P<0.001
2069	609.79	71.58	2	1218.57	1.77	P<0.001
462	387.21	26.79	2	773.41	1.78	P<0.001
1784	565.27	79.16	4	2258.06	1.78	P<0.001
1487	519.74	46.69	2	1038.47	1.83	P<0.05
15	304.5	23.36	3	911.48	1.85	P<0.05
967	448.75	39.11	2	896.49	1.88	P<0.05
3617	663.26	67.78	4	2650.02	1.89	P<0.05
2887	878.41	56.31	2	1755.81	1.89	NA
1841	573.24	50.05	5	2862.17	1.92	P<0.05
2189	631.96	59.7	3	1893.86	1.93	P<0.01
3138	330.18	30.36	2	659.35	1.93	P<0.05
2616	744.34	62.03	3	2231	1.96	P<0.01
507	393.55	31.7	3	1178.63	2.03	P<0.01
4386	583.08	52.02	5	2911.37	2.05	P<0.01
2076	611.31	25.89	1	611.31	2.08	CountDiff
3066	1110.59	50.12	1	1110.59	2.1	P<0.001

Table 6. Unidentified Proteins Decreased in Subjects having RA

Component #	m/z	R.T.(min.)	z	M+H	Fold Change	P
318	364.95	23.48	5	1820.72	-1	CountDiff
1241	484.26	54.27	2	967.51	-1.01	CountDiff
3903	837.4	27.47	1	837.4	-1.01	CountDiff
83	320.78	31.6	3	960.32	-1.02	CountDiff
3661	689.29	60.49	2	1377.57	-1.06	CountDiff
3690	700.02	64.51	3	2098.04	-1.08	CountDiff
3932	857.36	47.86	1	857.36	-1.08	CountDiff
4115	1131.12	57.28	3	3391.34	-1.08	CountDiff
551	400.19	15.89	2	799.37	-1.09	CountDiff
4071	1025.1	59.01	3	3073.28	-1.09	CountDiff
2504	710.85	47.1	1	710.85	-1.1	P<0.01
4747	1116.4	39.7	5	5577.97	-1.1	CountDiff
3230	459.86	60.4	3	1377.56	-1.1	CountDiff
1139	471.73	42.23	2	942.45	-1.11	P<0.05
4025	958.73	90.27	3	2874.17	-1.11	CountDiff
2653	754.33	68.05	3	2260.97	-1.12	CountDiff
602	407.26	42.79	1	407.26	-1.13	P<0.01
3677	695.01	68.99	3	2083.01	-1.13	CountDiff
3599	655.95	58.61	3	1965.83	-1.13	CountDiff
2209	634.34	67.94	3	1901	-1.13	CountDiff
756	426.2	46.65	3	1276.58	-1.14	P<0.01
2410	687.82	51.52	2	1374.63	-1.14	P<0.05
4446	638.34	62.21	3	1913	-1.14	CountDiff
274	357.18	27.64	2	713.35	-1.15	P<0.05
3161	394.68	42.76	1	394.68	-1.15	P<0.05

Component #	m/z	R.T.(min.)	z	M+H	Fold Change	P
4743	656.85	60.16	2	1312.69	-1.15	CountDiff
4132	1186.96	69.82	4	4744.82	-1.16	P<0.005
2014	600.28	44.19	1	600.28	-1.16	P<0.01
2167	628.31	42.75	2	1255.61	-1.16	P<0.05
1005	453.26	55.38	1	453.26	-1.16	CountDiff
209	346.13	47.08	3	1036.37	-1.17	P<0.01
1833	572.73	36.07	1	572.73	-1.17	P<0.05
896	441.17	47.81	3	1321.49	-1.18	P<0.005
3637	670.83	56.54	2	1340.65	-1.18	P<0.05
1791	566.28	63.12	3	1696.82	-1.18	P<0.05
3352	529.91	34.65	3	1587.71	-1.18	P<0.05
3319	514.72	44.77	4	2055.86	-1.18	P<0.05
3547	632.27	60.49	4	2526.06	-1.18	CountDiff
2690	769.43	34.83	1	769.43	-1.18	CountDiff
1553	528.46	60.79	4	2110.82	-1.19	P<0.01
1622	540.27	52.88	3	1618.79	-1.19	P<0.01
2041	605.28	60.14	2	1209.55	-1.19	CountDiff
3185	416.25	29.14	1	416.25	-1.2	P<0.001
781	429.21	45.22	3	1285.61	-1.2	P<0.01
3743	737.28	60.1	5	3682.37	-1.2	P<0.01
639	411.83	44.17	3	1233.47	-1.2	P<0.05
1888	579.7	10.11	2	1158.39	-1.2	P<0.05
1616	539.52	53.43	3	1616.54	-1.2	P<0.05
3814	778.32	58.9	2	1555.63	-1.2	P<0.05
705	420.2	46.68	3	1258.58	-1.21	P<0.001
2242	638.81	46.68	2	1276.61	-1.21	P<0.005
361	372.17	53.7	2	743.33	-1.21	P<0.01
1684	551.26	62.19	3	1651.76	-1.21	P<0.05
2644	752.77	29.66	2	1504.53	-1.21	P<0.05
3653	682.8	66.48	2	1364.59	-1.21	P<0.05
2476	704.3	60.83	3	2110.88	-1.21	P<0.05
3302	503.27	62.28	2	1005.53	-1.21	CountDiff
822	432.54	41.74	3	1295.6	-1.22	P<0.001
933	445.22	25.58	2	889.43	-1.22	P<0.05
3196	422.24	41.17	2	843.47	-1.22	P<0.05
3282	497.2	26.65	2	993.39	-1.22	P<0.05
1037	459.26	16.88	1	459.26	-1.23	P<0.001
1526	524.78	52.11	2	1048.55	-1.23	P<0.005
412	381.2	37.13	2	761.39	-1.23	P<0.05
1886	579.3	39.98	1	579.3	-1.23	CountDiff
1803	568.34	28.91	1	568.34	-1.24	P<0.05
2321	659.29	38.31	2	1317.57	-1.24	P<0.05
2150	625.79	51.25	2	1250.57	-1.25	P<0.005
2454	698.96	60.79	3	2094.86	-1.25	P<0.05
30	308.65	23.12	2	616.29	-1.25	P<0.05
3786	758.81	61.48	4	3032.22	-1.25	P<0.05
708	420.69	39.39	2	840.37	-1.26	P<0.005

Component #	m/z	R.T.(min.)	z	M+H	Fold Change	P
3528	627.76	31.87	2	1254.51	-1.26	P<0.05
2627	746.39	54.08	2	1491.77	-1.26	P<0.05
4315	504.3	59.03	1	504.3	-1.26	CountDiff
3847	796.32	63.29	2	1591.63	-1.27	P<0.01
3993	926.85	60.09	4	3704.38	-1.27	P<0.01
3559	636.29	50.39	2	1271.57	-1.27	P<0.05
1865	575.79	48.26	2	1150.57	-1.27	P<0.05
2346	669.35	52.81	1	669.35	-1.27	CountDiff
4720	868.39	95.83	3	2603.15	-1.28	P<0.01
1339	499.17	30.18	3	1495.49	-1.28	P<0.05
544	399.5	29.97	3	1196.48	-1.28	P<0.05
3093	1181.18	69.83	4	4721.7	-1.28	P<0.05
3231	460.86	66.48	3	1380.56	-1.29	P<0.001
1523	524.53	58.91	3	1571.57	-1.29	P<0.001
1343	499.71	41.52	4	1995.82	-1.29	P<0.001
1582	533.92	72.35	3	1599.74	-1.29	P<0.005
956	447.55	56.59	3	1340.63	-1.29	P<0.01
2228	637.29	57.29	3	1909.85	-1.29	P<0.05
569	402.18	39.56	4	1605.7	-1.29	P<0.05
3460	593.86	46.52	3	1779.56	-1.29	P<0.05
734	424.2	27.4	2	847.39	-1.29	NA
3247	471.16	36.96	3	1411.46	-1.3	P<0.005
3385	554.64	49.15	3	1661.9	-1.3	P<0.005
2207	634.28	52.68	3	1900.82	-1.3	P<0.005
1471	518.28	55.64	2	1035.55	-1.3	P<0.01
3513	620.49	38	4	2478.94	-1.3	P<0.01
2601	739.98	67.12	3	2217.92	-1.3	P<0.05
1388	505.74	46.01	2	1010.47	-1.31	P<0.005
1676	549.26	52.42	2	1097.51	-1.32	P<0.005
1416	510.6	62.03	3	1529.78	-1.32	P<0.01
4393	588.07	60.25	5	2936.32	-1.32	CountDiff
4273	467.51	49.21	3	1400.51	-1.32	CountDiff
1949	589.9	46.06	3	1767.68	-1.33	P<0.001
979	450.21	41.32	2	899.41	-1.33	P<0.005
1619	539.94	50.88	3	1617.8	-1.34	P<0.005
1083	465.18	60.43	3	1393.52	-1.34	P<0.005
4268	463.71	31.67	1	463.71	-1.34	P<0.005
948	446.57	45.93	3	1337.69	-1.34	P<0.005
2492	709.28	60.78	1	709.28	-1.34	P<0.01
623	409.65	11.88	2	818.29	-1.34	P<0.05
3922	848.59	57.28	4	3391.34	-1.34	P<0.05
922	444.2	46.5	4	1773.78	-1.34	P<0.05
1893	580.27	37.89	2	1159.53	-1.35	P<0.005
3375	543.28	41.64	2	1085.55	-1.35	P<0.01
1459	516.76	36.71	2	1032.51	-1.35	P<0.05
1219	480.95	54.37	4	1920.78	-1.36	P<0.001
1501	521.5	69.02	4	2082.98	-1.36	P<0.001

Component #	m/z	R.T.(min.)	z	M+H	Fold Change	P
3028	1022.75	58.92	3	3066.23	-1.36	P<0.05
3379	547.79	41.79	2	1094.57	-1.36	P<0.05
2175	629.28	36.79	1	629.28	-1.36	P<0.05
1480	519.21	58.92	3	1555.61	-1.37	P<0.001
2386	681.32	59.85	1	681.32	-1.37	P<0.01
1545	527.57	48.59	3	1580.69	-1.37	P<0.05
2135	624.28	66.75	3	1870.82	-1.37	P<0.05
1583	533.97	50.62	4	2132.86	-1.38	P<0.01
468	387.71	36	4	1547.82	-1.38	P<0.05
1500	521.32	49.35	1	521.32	-1.39	P<0.05
2687	768.41	65.45	1	768.41	-1.39	P<0.05
4507	745.7	38.35	2	1490.39	-1.39	P<0.05
3813	777.73	29.64	2	1554.45	-1.39	P<0.05
534	397.65	23.95	2	794.29	-1.4	P<0.005
3916	845.86	64.65	2	1690.71	-1.41	P<0.05
333	366.68	25.31	2	732.35	-1.42	P<0.005
4233	421.68	62.22	4	1683.7	-1.42	P<0.05
4522	842.36	62.23	2	1683.71	-1.43	P<0.005
4715	729.06	70.36	4	2913.22	-1.43	P<0.01
4515	797.8	58.98	2	1594.59	-1.44	P<0.005
1623	540.27	51.25	3	1618.79	-1.46	P<0.001
2412	688.74	34.24	2	1376.47	-1.48	P<0.01
1682	550.32	46.09	1	550.32	-1.48	P<0.05
4485	715.23	43.15	3	2143.67	-1.48	P<0.05
2066	609.3	48.71	1	609.3	-1.48	P<0.05
4451	644.3	44.82	3	1930.88	-1.49	P<0.05
4454	646.63	57.7	3	1937.87	-1.5	P<0.05
3152	356.5	55.62	3	1067.48	-1.5	P<0.05
1028	458.22	33.59	1	458.22	-1.51	P<0.001
3357	532.2	59.04	3	1594.58	-1.51	P<0.05
351	369.71	35.73	2	738.41	-1.52	P<0.05
2413	688.78	34.81	2	1376.55	-1.53	NA
811	431.88	36.99	3	1293.62	-1.54	P<0.05
1513	522.95	51.24	3	1566.83	-1.55	P<0.01
1013	454.73	42.15	2	908.45	-1.56	P<0.005
683	417.7	28.98	2	834.39	-1.56	P<0.005
919	444.19	34.05	2	887.37	-1.56	P<0.05
790	429.85	50.45	3	1287.53	-1.57	P<0.05
3360	534.26	55.63	2	1067.51	-1.58	P<0.05
2020	601.27	54.07	2	1201.53	-1.58	P<0.05
2485	707.8	68.94	2	1414.59	-1.59	P<0.05
246	352.14	42.14	3	1054.4	-1.59	P<0.05
1208	480.23	52.23	2	959.45	-1.59	P<0.05
1324	496.9	53.03	3	1488.68	-1.59	P<0.05
1557	529.28	47.26	2	1057.55	-1.61	P<0.005
606	407.7	29.3	2	814.39	-1.61	P<0.05
4126	1176.92	73.99	4	4704.66	-1.62	P<0.001

Component #	m/z	R.T.(min.)	z	M+H	Fold Change	P
1179	475.74	51.59	2	950.47	-1.63	P<0.05
1145	472.47	41.83	4	1886.86	-1.66	P<0.05
2648	753.26	51.11	2	1505.51	-1.7	P<0.005
891	440.21	53.63	2	879.41	-1.71	P<0.005
3365	536.68	43.17	4	2143.7	-1.73	P<0.05
4238	429.67	53.75	4	1715.66	-1.75	P<0.005
1330	497.77	46.04	2	994.53	-1.78	CountDiff
2341	668.33	54.87	1	668.33	-1.83	P<0.001
147	334.66	54.92	2	668.31	-1.83	CountDiff
1595	536.27	58.54	2	1071.53	-1.85	P<0.005
276	357.2	31.12	2	713.39	-1.85	P<0.05
4329	519.55	56.49	3	1556.63	-1.86	P<0.05
989	451.69	31.31	2	902.37	-1.89	CountDiff
4187	344.8	38.35	3	1032.38	-1.95	P<0.05
4328	517.71	41.31	2	1034.41	-1.96	P<0.05
3263	483.45	44.81	4	1930.78	-1.99	P<0.05
3953	882.4	47.02	2	1763.79	-2	P<0.01
1566	531.71	48.59	2	1062.41	-2.02	P<0.001
4327	516.7	38.34	2	1032.39	-2.03	P<0.05
3523	625.23	34.1	3	1873.67	-2.04	P<0.005
625	409.71	35.09	2	818.41	-2.05	P<0.001
2395	683.33	64.51	1	683.33	-2.07	P<0.001
1097	466.75	48.7	2	932.49	-2.08	P<0.005
189	342.16	64.49	2	683.31	-2.13	P<0.005
484	389.22	34.35	2	777.43	-2.13	P<0.01
4172	301.12	46.02	2	601.23	-2.28	P<0.05
4179	323.14	48.38	2	645.27	-2.32	P<0.01
2819	835.38	71.65	4	3338.5	-2.32	P<0.05
373	373.74	75.12	2	746.47	-2.47	P<0.001

Table 7. Cell Populations Increased in Subjects having RA

Study	General Cell Type	Assay	Cell Population	Property	p	adjp	Effect Size
Study2	B cell subset	CD69_CD71_CD20	CD20pCD69p/CD20p	RATIO	0.034	1	0.2562762
Study 1	B Cell subset	CD69_CD71_CD20v4	CD20pCD71p/CD20p	RATIO	0.000028	0.017111	0.9447959
Study2	CD4 T Cell subset	CD26_CD4_CD3	CD3pCD4pCD26p/CD3pCD4p	RATIO	<0.001	0.594	0.7056072
Study2	CD4 T Cell subset	CD101_CD14_CD4	CD4pCD14nCD101p	COUNT	<0.001	0.471	0.6725686
Study2	CD4 T Cell subset	CD101_CD14_CD4	CD4pCD14nCD101p/CD4pCD14n	RATIO	<0.001	0.012	0.8145183
Study2	CD4 T Cell subset	CD25_CD14_CD4	CD4pCD14nCD25p/CD4pCD14n	RATIO	0.027	1	0.4226701
Study2	CD4 T Cell subset	CD38_CD14_CD4	CD4pCD14nCD38p/CD4pCD14n	RATIO	0.015	1	0.5438194
Study2	CD4 T Cell subset	CD71_CD14_CD4	CD4pCD14nCD71p	COUNT	0.004	1	0.4125228
Study2	CD4 T Cell subset	CD71_CD14_CD4	CD4pCD14nCD71p/CD4pCD14n	RATIO	0.002	1	0.3309689
Study 1	CD4 T Cell subset	CD45RB_CD27_CD4v3	CD4pCD27pCD45RBp	COUNT	0.009331	1.000000	0.4183194
Study2	CD4 T Cell subset	CD28_CD45RA_CD4	CD4pCD28pCD45RAp/CD4p	RATIO	0.006	1	0.5449754
Study2	CD4 T Cell subset	CD62L_CD45RA_CD4	CD4pCD45RApCD62Lp/CD4p	RATIO	0.022	1	0.4697498
Study2	CD4 T Cells	CD4_CD8_CD3	CD4 T cells/T cells	RATIO	<0.001	0.027	0.8437971
Study 1	CD4 T Cells	AVERAGE	CD4 T cells/T cells	RATIO	0.000002	0.001481	0.8474299
Study2	CD8 T Cell subset	CD57_CD6_CD8	CD6pCD8pCD57p/CD6pCD8p	RATIO	0.012	1	0.4859035
Study2	CD8 T Cell subset	CD26_CD7_CD8	CD7pCD8pCD26p/CD7pCD8p	RATIO	0.026	1	0.4544495
Study2	CD8 T Cell subset	CD38_CD20_CD8	CD8pCD20nCD38p/CD8pCD20n	RATIO	0.002	1	0.710085
Study 1	CD8 T cell subset	CD95_CD20_CD8v3	CD8pCD20nCD95p/CD8pCD20n	RATIO	0.037409	1.000000	0.3435766
Study 1	CD8 T cell subset	CD69_CD25_CD8v9	CD8pCD25p/CD8p	RATIO	0.011157	1.000000	0.4500325
Study2	CD8 T Cell subset	CD69_CD25_CD8	CD8pCD25p/CD8p	RATIO	0.018	1	0.5885806
Study2	CD8 T Cell subset	CD28_CD62L_CD8	CD8pCD28nCD62Lp/CD8p	RATIO	0.027	1	0.2799138
Study2	CD8 T Cell subset	CD28_CD62L_CD8	CD8pCD28pCD62Lp/CD8p	RATIO	0.023	1	0.3682324
Study2	CD8 T Cell subset	CD161_CD45RA_CD8	CD8pCD45RApCD161p/CD8p	RATIO	0.034	1	0.3000852
Study2	CD8 T Cell subset	CD60_CD45RA_CD8	CD8pCD45RApCD60p/CD8p	RATIO	0.046	1	0.3834613
Study2	CD8 T Cell subset	CD62L_CD45RA_CD8	CD8pCD45RApCD62Lp/CD8p	RATIO	0.023	1	0.5056861
Study 1	CD8 T cell subset	CD71_CD57_CD8v7	CD8pCD57p/CD8p	RATIO	0.023666	1.000000	0.4121008
Study2	CD8 T Cell subset	CD69_CD25_CD8	CD8pCD69p/CD8p	RATIO	0.004	1	0.5096072
Study2	CD8 T Cell subset	CD71_CD57_CD8	CD8pCD71p/CD8p	RATIO	<0.001	0.225	0.5837997
Study 1	Eosinophils	AVERAGE	Eosinophils	COUNT	0.049423	1.000000	0.2972259
Study 1	Ganulocytes	AVERAGE	Granulocytes/WBC	RATIO	0.002313	1.000000	0.5760901

Study	General Cell Type	Assay	Cell Population	Property	p	adjp	Effect Size
Study 1	Ganulocytes subset	CD52_CD66b_CD16v10	CD16pCD66bpCD52n	COUNT	0.000839	0.490015	0.6358233
Study 1	Granulocyet subset	CD89_CD15_CD14v13	CD14nCD15pCD89p	COUNT	0.010515	1.000000	0.4998616
Study2	Granulocyte	CD45_CD14_CD16	CD14nCD16pCD45p/CD45p	RATIO	<0.001	0.159	0.6611517
Study2	Granulocyte subset	CD32_CD11b_CD16	CD11bpCD16p	COUNT	<0.001	0.522	0.6897164
Study2	Granulocyte subset	CD32_CD11b_CD16	CD11bpCD16pCD32p	COUNT	<0.001	0.314	0.7209454
Study2	Granulocyte subset	CD89_CD15_CD14	CD14nCD15pCD89p	COUNT	0.004	1	0.606532
Study 1	Granulocyte subset	CD64_CD14_CD16v11	CD14nCD16pCD64n	COUNT	0.004652	1.000000	0.5420431
Study2	Granulocyte subset	CD44_CD18_CD16	CD16pCD18pCD44p	COUNT	0.002	0.832	0.662342
Study 1	Granulocytes	AVERAGE	Granulocytes	COUNT	0.003999	1.000000	0.5622894
Study2	Granulocytes	CD45_CD14_CD16	Granulocytes	COUNT	<0.001	0.417	0.6978234
Study2	Leukocytes	CD45_CD14_CD16	CD45p	COUNT	0.005	1	0.5891922
Study 1	Leukocytes	AVERAGE	WBC	COUNT	0.022359	1.000000	0.4339659
Study 1	Monocyte subset	CCR5_CD60_CD14v9	CCR5nCD14pCD60n	COUNT	0.000018	0.011226	0.8008547
Study2	Monocyte subset	CD89_CD15_CD14	CD14pCD15n	COUNT	0.02	1	0.4712457
Study2	Monocyte subset	CD89_CD15_CD14	CD14pCD15nCD89p	COUNT	0.023	1	0.3803188
Study 1	Monocyte subset	CD89_CD15_CD14v13	CD14pCD15nCD89p	COUNT	0.000067	0.040736	0.7798395
Study 1	Monocyte subset	CD119_CD14_CD16v6	CD14pCD16nCD119n	COUNT	0.002333	1.000000	0.5632859
Study2	Monocyte subset	CD64_CD14_CD16	CD14pCD16nCD64p	COUNT	0.033	1	0.4669147
Study2	Monocyte subset	CD40_CD14_CD20	CD14pCD20nCD40n/CD14pCD20n	RATIO	0.003	1	0.6391118
Study 1	Monocyte subset	CD62L_CD14_CD20v7	CD14pCD20nCD62Ln	COUNT	0.000349	0.206385	0.7185618
Study2	Monocyte subset	HLADP_CD14_CD20	CD14pCD20nDPn	COUNT	0.006	1	0.5451047
Study2	Monocyte subset	HLADQ_CD14_CD20	CD14pCD20nDQn	COUNT	<0.001	0.199	0.8248779
Study2	Monocyte subset	HLADQ_CD14_CD20	CD14pCD20nDQt	COUNT	0.017	1	0.4817503
Study2	Monocyte subset	HLADR4_CD14_CD20	CD14pCD20nDR4n	COUNT	<0.001	0.214	0.6198077
Study2	Monocyte subset	HLADR_CD14_CD20	CD14pCD20nDRn	COUNT	<0.001	0.706	0.5486261
Study 1	Monocyte subset	HLADP_CD14_CD20v8	CD14pCD20nHLADPn	COUNT	0.000496	0.290933	0.7591109
Study 1	Monocyte subset	HLADQ_CD14_CD20v8	CD14pCD20nHLADQn	COUNT	0.001188	0.686415	0.7638421
Study 1	Monocyte subset	HLADR_CD14_CD20v9	CD14pCD20nHLADRp	COUNT	0.000187	0.111461	0.6868374

Study	General Cell Type	Assay	Cell Population	Property	p	adjp	Effect Size
Study 1	Monocyte subset	HLAPAN_CD14_CD20v7	CD14pCD20nHLAPANp	COUNT	0.000012	0.007617	0.8128984
Study2	Monocyte subset	HLAPAN_CD14_CD20	CD14pCD20nPANt	COUNT	0.044	1	0.4641527
Study2	Monocyte subset	CCR5_CD60_CD14	CD14pCD60n	COUNT	0.014	1	0.5367433
Study 1	Monocyte subset	TLR4_CD33_CD20v2	CD20nCD33pTLR4p/CD20nCD33p	RATIO	0.001021	0.593409	0.3967629
Study 1	Monocyte subset	CD54_CD14_CD3v10	CD3nCD14pCD54n	COUNT	0.005090	1.000000	0.5809295
Study 1	Monocyte subset	CD54_CD14_CD3v10	CD3nCD14pCD54p	COUNT	0.036752	1.000000	0.4551894
Study2	Monocyte subset	CD26_CD4_CD3	CD3pCD4pCD26p	COUNT	0.015	1	0.2978743
Study 1	Monocyte subset	CD101_CD14_CD4v3	CD4pnCD14pCD101n	COUNT	0.000073	0.043861	0.7771187
Study2	Monocyte subset	CD33_CD14_CD4	CD4pnCD14pCD33p	COUNT	0.02	1	0.4861742
Study 1	Monocyte subset	CD38_CD14_CD4v10	CD4pnCD14pCD38n	COUNT	0.044678	1.000000	0.4373296
Study 1	Monocyte subset	CD38_CD14_CD4v10	CD4pnCD14pCD38p	COUNT	0.015898	1.000000	0.5011491
Study 1	Monocyte subset	CD86_CD14_CD4v6	CD4pnCD14pCD86n	COUNT	0.000042	0.025753	0.784163
Study2	Monocyte subset	CD95_CD4_CD14	CD4pnCD14pCD95t	COUNT	0.014	1	0.572237
Study2	Monocytes	CD45_CD14_CD16	CD14pCD16nCD45p	COUNT	0.028	1	0.3914396
Study 1	Monocytes	CD64_CD14_CD16v11	CD14pCD16nCD64p	COUNT	0.000015	0.008968	0.8132311
Study2	Monocytes	CD40_CD14_CD20	CD14pCD20nCD40n	COUNT	<0.001	0.301	0.7881695
Study 1	Monocytes	AVERAGE	Monocytes	COUNT	0.000003	0.001611	0.8927377
Study 1	Monocytes	AVERAGE	Monocytes/WBC	RATIO	0.000861	0.502040	0.6049538
Study 1	Neutrophils	CD32_CD11b_CD16v4	CD11bpCD16n	COUNT	0.000003	0.001626	0.5854824
Study 1	Neutrophils	AVERAGE	Neutrophils	COUNT	0.012507	1.000000	0.4841396
Study 1	Neutrophils	AVERAGE	Neutrophils/WBC	RATIO	0.010949	1.000000	0.3581328
Study 1	NK cell subset	CD161_CD56_CD3v2	CD3nCD56pCD161n	COUNT	0.002574	1.000000	0.5537043
Study 1	Other	CD52_CD66b_CD16v10	CD16nCD66bpCD52p	COUNT	0.039894	1.000000	0.423507
Study2	T cell subset	TCRab_TCRgd_CD3	CD3pTCRabp/CD3pTCRgdp	RATIO	0.031	1	0.2495411
Study 1	T Cell subset	AVERAGE	CD4 T cells/CD8 T cells	RATIO	0.000000	0.000125	0.9125348
Study2	T Cells subset	CD4_CD8_CD3	CD3pCD4p/CD3pCD8p	RATIO	<0.001	0.011	0.739175

Table 8. Cell Populations Decreased in Subjects having RA

Study	General Cell Type	Assay	Cell Population	Property	p	adjp	Effect Size
Study 1	B cell subet	CD38_CD20_CD8v8	CD8nCD20pCD38p	COUNT	0.002862	1.000000	0.3682915
Study 1	B cell subset	CD62L_CD14_CD20v7	CD14nCD20pCD62Lp	COUNT	0.028677	1.000000	0.3458029
Study2	B cell subset	CD95_CD20_CD8	CD8nCD20pCD95p/CD8nCD20p	RATIO	0.044	1	0.5172224
Study 1	CD4 T Cell subset	CCR5_CD60_CD4v8	CCR5pCD4pCD60n	COUNT	0.039289	1.000000	0.143363
Study2	CD4 T Cell subset	CCR5_CD60_CD4	CCR5pCD4pCD60n	COUNT	<0.001	0.484	0.6594824
Study2	CD4 T Cell subset	CCR5_CD60_CD4	CCR5pCD4pCD60p	COUNT	0.02	1	0.6180808
Study 1	CD4 T Cell subset	CCR5_CD60_CD4v8	CCR5pCD4pCD60p	COUNT	0.000003	0.001971	0.8299302
Study2	CD4 T Cell subset	CCR5_CD60_CD4	CCR5pCD4pCD60p/CD4pCD60p	RATIO	0.044	1	0.5271522
Study2	CD4 T Cell subset	CD26_CD4_CD3	CD3pCD4nCD26p	COUNT	<0.001	0.582	0.6011615
Study2	CD4 T Cell subset	CD71_CD14_CD4	CD4pCD14nCD71n	INTENSITY2	0.037	1	0.2079245
Study 1	CD4 T Cell subset	CD45RB_CD27_CD4v3	CD4pCD27nCD45RBpn	COUNT	0.000339	0.201163	0.6604196
Study2	CD4 T Cell subset	CD28_CD45RA_CD4	CD4pCD28nCD45RAn	COUNT	0.024	1	0.5365788
Study 1	CD4 T Cell subset	CD62L_CD45RA_CD4v10	CD4pCD45RAnCD62Ln	COUNT	0.020345	1.000000	0.2301247
Study2	CD4 T Cell subset	CD62L_CD45RA_CD4	CD4pCD45RAnCD62Ln	COUNT	0.003	1	0.5810947
Study2	CD4 T Cell subset	CCR5_CD60_CD4	CD4pCD60n	COUNT	0.005	1	0.3887799
Study 1	CD8 T cell subset	CCR5_CD60_CD8v10	CCR5nCD8pCD60n	COUNT	0.000340	0.201163	0.5948072
Study 1	CD8 T cell subset	CCR5_CD60_CD8v10	CCR5pCD8nCD60p	COUNT	0.000154	0.091844	0.648314
Study 1	CD8 T cell subset	CCR5_CD60_CD8v10	CCR5pCD8pCD60n	COUNT	0.000220	0.131181	0.5630113
Study2	CD8 T Cell subset	CCR5_CD60_CD8	CCR5pCD8pCD60n	COUNT	<0.001	0.55	0.6738924
Study 1	CD8 T cell subset	CCR5_CD60_CD8v10	CCR5pCD8pCD60p	COUNT	0.000083	0.049881	0.6799198
Study 1	CD8 T cell subset	CD57_CD6_CD8v7	CD6pCD8pCD57n	COUNT	0.000021	0.013126	0.7616691
Study 1	CD8 T cell subset	CD57_CD6_CD8v7	CD6pCD8pCD57p	COUNT	0.034692	1.000000	0.2409203
Study 1	CD8 T cell subset	CD26_CD7_CD8v6	CD7pCD8pCD26n	COUNT	0.000040	0.024211	0.6693274
Study 1	CD8 T cell subset	CD26_CD7_CD8v6	CD7pCD8pCD26p	COUNT	0.000007	0.004312	0.7044912
Study2	CD8 T Cell subset	CD26_CD7_CD8	CD7pCD8pn	COUNT	0.049	1	0.2474836
Study 1	CD8 T cell subset	CD26_CD7_CD8v6	CD7pCD8pnCD26p	COUNT	0.000000	0.000174	0.5913666
Study 1	CD8 T cell subset	CD101_CD8_CD16v4	CD8pCD16nCD101n	COUNT	0.000006	0.003846	0.7599001

Study	General Cell Type	Assay	Cell Population	Property	p	adjp	Effect Size
Study 1	CD8 T cell subset	CD101_CD8_CD16v4	CD8pCD16nCD101p	COUNT	0.001030	0.597433	0.5640556
Study2	CD8 T Cell subset	CD101_CD8_CD16	CD8pCD16nCD101p	COUNT	0.018	1	0.5640679
Study 1	CD8 T cell subset	CD38_CD20_CD8v8	CD8pCD20nCD38n	COUNT	0.000083	0.049859	0.5750184
Study 1	CD8 T cell subset	CD38_CD20_CD8v8	CD8pCD20nCD38p	COUNT	0.002985	1.000000	0.6074203
Study2	CD8 T Cell subset	CD44_CD20_CD8	CD8pCD20nCD44p/CD8pCD20n	RATIO	0.003	1	0.6407937
Study2	CD8 T Cell subset	CD95_CD20_CD8	CD8pCD20nCD95p	COUNT	0.002	1	0.5072614
Study2	CD8 T Cell subset	CD27_CD45RA_CD8	CD8pCD27nCD45RAp	COUNT	0.023	1	0.2520115
Study2	CD8 T Cell subset	CD27_CD45RA_CD8	CD8pCD27pCD45RAp	COUNT	0.024	1	0.2149937
Study 1	CD8 T cell subset	CD28_CD62L_CD8v12	CD8pCD28nCD62Ln	COUNT	0.002633	1.000000	0.4409627
Study2	CD8 T Cell subset	CD28_CD62L_CD8	CD8pCD28pCD62Ln	COUNT	<0.001	0.554	0.6604842
Study 1	CD8 T cell subset	CD28_CD62L_CD8v12	CD8pCD28pCD62Ln	COUNT	0.000000	0.000270	1.1057356
Study2	CD8 T Cell subset	CD28_CD62L_CD8	CD8pCD28pCD62Ln/CD8p	RATIO	0.02	1	0.3431341
Study2	CD8 T Cell subset	CD60_CD45RA_CD8	CD8pCD45RAnCD60n	COUNT	<0.001	0.054	0.9521301
Study 1	CD8 T cell subset	CD62L_CD45RA_CD8v7	CD8pCD45RAnCD62Ln	COUNT	0.000000	0.000223	0.8592887
Study2	CD8 T Cell subset	CD62L_CD45RA_CD8	CD8pCD45RAnCD62Ln	COUNT	<0.001	0.021	0.8769976
Study 1	CD8 T cell subset	CD62L_CD45RA_CD8v7	CD8pCD45RAnCD62Lp	COUNT	0.010010	1.000000	0.4030196
Study2	CD8 T Cell subset	CD161_CD45RA_CD8	CD8pCD45RApCD161n	COUNT	0.039	1	0.2853463
Study2	CD8 T Cell subset	CD60_CD45RA_CD8	CD8pCD45RApCD60n	COUNT	0.027	1	0.3142181
Study 1	CD8 T cell subset	CD62L_CD45RA_CD8v7	CD8pCD45RApCD62Ln	COUNT	0.001431	0.821474	0.3975255
Study2	CD8 T Cell subset	CD62L_CD45RA_CD8	CD8pCD45RApCD62Ln	COUNT	0.004	1	0.4458392
Study 1	CD8 T cell subset	CD62L_CD45RA_CD8v7	CD8pCD45RApCD62Lp	COUNT	0.000970	0.564536	0.6330695
Study2	CD8 T Cell subset	CD71_CD57_CD8	CD8pCD57n	COUNT	<0.001	0.122	0.7908748
Study 1	CD8 T cell subset	CD94_CD57_CD8v2	CD8pCD57nCD94n	COUNT	0.000466	0.273881	0.7045932
Study 1	CD8 T cell subset	CD94_CD57_CD8v2	CD8pCD57nCD94p	COUNT	0.038480	1.000000	0.3735341
Study2	CD8 T Cell subset	CD71_CD57_CD8	CD8pCD57p	COUNT	0.003	1	0.6847291
Study 1	CD8 T cell subset	CD94_CD57_CD8v2	CD8pCD57pCD94n	COUNT	0.004381	1.000000	0.2096493
Study2	CD8 T Cell subset	CD69_CD25_CD8	CD8pCD69n	COUNT	<0.001	0.161	0.7076249
Study2	CD8 T Cell subset	CD71_CD57_CD8	CD8pCD71n	COUNT	<0.001	0.009	0.9965162
Study2	CD8 T Cells	AVERAGE	CD8 T cells	COUNT	<0.001	0.14	0.6295512
Study 1	CD8 T Cells	AVERAGE	CD8 T cells	COUNT	0.000003	0.002003	0.8110482

Study	General Cell Type	Assay	Cell Population	Property	p	adjp	Effect Size
Study2	CD8 T cells	CD4_CD8_CD3	CD8 T cells/T cells	RATIO	<0.001	0.008	0.9017942
Study 1	CD8 T Cells	AVERAGE	CD8 T cells/T cells	RATIO	0.000000	0.000151	1.037131
Study 1	CD8 T Cells	AVERAGE	CD8 T cells/WBC	RATIO	0.000000	0.000011	1.1785306
Study2	Lymphocyte	CD45_CD14_CD16	CD14nCD16nCD45p/CD45p	RATIO	<0.001	0.125	0.6246031
Study 1	Lymphocytes	AVERAGE	Lymphocytes/WBC	RATIO	0.001382	0.795972	0.4419753
Study2	Monocyte subset	CD40_CD14_CD20	CD14pCD20nCD40pn	COUNT	0.021	1	0.3695376
Study2	Monocyte subset	CD40_CD14_CD20	CD14pCD20nCD40pn/CD14pCD20n	RATIO	0.003	1	0.6390621
Study2	Monocyte subset	HLADP_CD14_CD20	CD14pCD20nDPp/CD14pCD20n	COUNT	0.009	1	0.5748591
Study2	Monocyte subset	HLADQ_CD14_CD20	CD14pCD20nDQp	COUNT	0.028	1	0.3862537
Study2	Monocyte subset	HLADQ_CD14_CD20	CD14pCD20nDQp/CD14pCD20n	RATIO	0.003	1	0.6767177
Study2	Monocyte subset	HLADR_CD14_CD20	CD14pCD20nDRp/CD14pCD20n	RATIO	0.003	1	0.5615718
Study2	Monocyte subset	HLAPAN_CD14_CD20	CD14pCD20nPANp/CD14pCD20n	RATIO	0.017	1	0.5974805
Study2	Monocyte subset	CD54_CD14_CD3	CD3nCD14pCD54p/CD3nCD14p	COUNT	0.02	1	0.5385682
Study2	Monocyte subset	CD101_CD14_CD4	CD4pnCD14pCD101p/CD4pnCD14p	COUNT	0.038	1	0.439986
Study2	Monocyte subset	CD33_CD14_CD4	CD4pnCD14pCD33p/CD4pnCD14p	COUNT	0.017	1	0.3216624
Study2	Monocyte subset	CD86_CD14_CD4	CD4pnCD14pCD86p/CD4pnCD14p	COUNT	0.035	1	0.5365573
Study 1	Other	CCR5_CD60_CD14v9	CCR5pCD14nCD60p	COUNT	0.000043	0.025938	0.8062149
Study 1	Other	CCR5_CD60_CD4v8	CCR5pCD4nCD60p	COUNT	0.018091	1.000000	0.4447187
Study 1	Other	CD26_CD7_CD8v6	CD7pCD8pnCD26n	COUNT	0.005930	1.000000	0.2774447
Study 1	T Cell subset	CD158b_CD56_CD3v2	CD3pCD158bp	COUNT	0.043298	1.000000	0.1045154
Study 1	T Cell subset	CD161_CD56_CD3v2	CD3pCD161p	COUNT	0.001074	0.621719	0.5089205
Study 1	T cell subset	CD57_CD4_CD3v7	CD3pCD4nCD57p	COUNT	0.018212	1.000000	0.2056246
Study 1	T cell subset	CD94_CD56_CD3v2	CD3pCD94p	COUNT	0.019012	1.000000	0.2200139
Study2	T cell subset	TCRab_TCRgd_CD3	CD3pTCRgdp	COUNT	0.019	1	0.2370469
Study 1	T Cell subset	TCRab_TCRgd_CD3v8	CD3pTCRgdp	COUNT	0.000047	0.028634	0.3775772
Study 1	T Cell subset	CD7_CD6_CD4v7	CD4nCD6pCD7p	COUNT	0.000000	0.000261	0.8440452
Study2	T Cells	CD56_CD2_CD3	CD2pCD3p	COUNT	0.004	1	0.4343521
Study2	T Cells	NKB1_CD5_CD7	CD5pCD7pNKB1n	COUNT	0.016	1	0.2490271
Study 1	T cells	AVERAGE	T cells/WBC	RATIO	0.001407	0.808844	0.6047076